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## (12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property  
Organization  
International Bureau(43) International Publication Date  
29 January 2004 (29.01.2004)

PCT

(10) International Publication Number  
**WO 2004/009602 A1**(51) International Patent Classification<sup>7</sup>: **C07D 487/04**,  
519/00, A61K 31/519, A61P 3/10 // (C07D 487/04,  
239/00, 231/00)(21) International Application Number:  
PCT/US2003/022716

(22) International Filing Date: 21 July 2003 (21.07.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
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27709 (US).(81) Designated States (national): **AF, AG, AI, AM, AT, AU**,  
**AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU**,  
**CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GI**,  
**GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC**,  
**LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW**,  
**MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC**,  
**SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA**,  
**UG, US, UZ, VC, VN, YU, ZA, ZM, ZW**.(84) Designated States (regional): **ARIPO** patent (GH, GM,  
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),  
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),  
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,  
ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO,  
SE, SI, SK, TR), **OAPI** patent (BF, BJ, CF, CG, CI, CM,  
GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

## Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2004/009602 A1

(54) Title: **PYRAZOLOPYRIMIDINES AS KINASE INHIBITORS**

(57) Abstract: The present invention relates generally to inhibitors of the kinases and more particularly to novel pyrazolopyrimidine compounds.

## PYRAZOLOPYRIMIDINES AS KINASE INHIBITORS

### FIELD OF THE INVENTION

5           The present invention relates generally to inhibitors of the kinases, such as GSK3 or TIE2, and more particularly to novel pyrazolopyrimidine compounds.

### BACKGROUND OF THE INVENTION

10           The present invention provides compounds that are useful pharmacological agents for disease states that are mediated, for example alleviated, through the inhibition or antagonism, of protein kinases. In particular, the present invention relates to compounds that demonstrate protein tyrosine kinase and/or protein serine/threonine kinase inhibition.

          The protein kinases represent a large family of proteins which play a central role in the regulation of a wide variety of cellular processes and maintaining control over cellular function (Hanks, *et al.*, Science, 1988, 241, 42-52). The loss of control over cellular regulation can often lead to aberrant cell function or death, often resulting in a disease state in the parent organism. A partial list of such kinases includes ab1, ATK, bcr-ab1, Blk, Brk, Btk, c-kit, c-met, c-src, CDK1, CDK2, CDK4, CDK6, cRaf1, CSF1R, CSK, EGFR, ErbB2, ErbB3, ErbB4, ERK, Fak, fes, FGFR1, FGFR2, FGFR3, FGFR4, FGFR5, Fgr, FLK-4, flt-1, Fps, Frk, Fyn, GSK3, Hck, IGF-1R, INS-R, Jak, KDR, Lck, Lyn, MEK, p38, PDGFR, PIK, PKC, PYK2, ros, TIE1, TIE2, TRK, Yes, and Zap70. Examples of kinase therapy include, but should not be limited to: (1) inhibition of c-Src (Brickell, Critical Reviews in Oncogenesis 1992, 3, 401-46; Courtneidge, Seminars in Cancer Biology 1994, 5, 239-46), raf (Powis, Pharmacology & Therapeutics 1994, 62, 57-95) and the cyclin-dependent kinases (CDKs) 1, 2 and 4 in cancer (Pines, Current Opinion in Cell Biology 1992, 4, 144-8; Lees, Current Opinion in Cell Biology 1995, 7, 773-80; Hunter and Pines, Cell 1994, 79, 573-82), (2) inhibition of CDK2 or PDGF-R kinase in restenosis (Buchdunger, *et al.*, Proceedings of the National Academy of Science USA 1995, 92, 2258-62), (3) inhibition of CDK5 and GSK3 kinases for Alzheimer's (Hosoi, *et al.*, Journal of Biochemistry (Tokyo) 1995, 117, 741-9; Aplin, *et al.*, Journal of Neurochemistry 1996, 67, 699-707), (4) inhibition of c-Src kinase in osteoporosis

(Tanaka, et al., *Nature* 1996, 383, 528-31), (5) inhibition of GSK-3 kinase in type-2 diabetes (Borthwick, et al., *Biochemical & Biophysical Research Communications* 1995, 210, 738-45), discussed in more detail below; (6) inhibition of the p38 kinase for inflammation (Badger, et al., *The Journal of Pharmacology and Experimental Therapeutics* 1996, 279, 1453-61); (7) inhibition of VEGF-R 1-3 and TIE-1 and -2 kinases in diseases which involve angiogenesis (Shawver, et al., *Drug Discovery Today* 1997, 2, 50-63); (8) inhibition of UL97 kinase in viral infections (He, et al., *Journal of Virology* 1997, 71, 405-11); (9) inhibition of CSF-1R kinase in bone and hematopoietic diseases (Myers, et al., *Bioorganic & Medicinal Chemistry Letters* 1997, 7, 421-4), and (10) inhibition of Lck kinase in autoimmune diseases and transplant rejection (Myers, et al., *Bioorganic & Medicinal Chemistry Letters* 1997, 7, 417-20).

Inhibitors of certain kinases may also have utility in the treatment of diseases when the kinase is not misregulated, but is nonetheless essential for maintenance of the disease state. In this case, inhibition of the kinase activity would act either as a cure or palliative for these diseases. For example, many viruses, such as human papilloma virus, disrupt the cell cycle and drive cells into the S-phase of the cell cycle (Vousden, *FASEB Journal* 1993, 7, 872-9). Preventing cells from entering DNA synthesis after viral infection by inhibition of essential S-phase initiating activities such as through kinase inhibition, may disrupt the virus life cycle by preventing virus replication. This same principle may be used to protect normal cells of the body from toxicity of cycle-specific chemotherapeutic agents (Stone, et al., *Cancer Research* 1996, 56, 3199-202; Kohn, et al., *Journal of Cellular Biochemistry* 1994, 54, 440-52).

As noted above, GSK3 (glycogen synthase kinase) is identified as a kinase useful in the treatment of type II diabetes. GSK3 inhibits glycogen synthase by direct phosphorylation. Upon insulin activation, GSK3 is inactivated, thereby allowing the activation of glycogen synthase and possibly other insulin-dependent events.

Type II diabetes, otherwise known as Non-Insulin Dependent Diabetes Mellitus (NIDDM), is initially characterized by decreased sensitivity to insulin (insulin resistance) and a compensatory elevation in circulating insulin concentrations. Increased insulin levels are caused by increased secretion from the pancreatic beta cells in an attempt to overcome the insulin resistance. The resulting hyperinsulinemia is associated with a variety of cardiovascular complications.

As insulin resistance worsens, the demand on the pancreatic beta cells steadily increases until the pancreas can no longer provide adequate levels of insulin, thereby resulting in elevated levels of glucose in the blood. Thus, diabetes causes impaired glucose transport into skeletal muscle and increased hepatic glucose production, in addition to inadequate insulin response. The disorders and conditions associated with hyperglycemia and hyperlipidemia include cardiovascular disease, renal failure, and blindness.

GSK3 inhibition stimulates insulin-dependent processes and is consequently useful in the treatment of diseases and conditions, such as type II diabetes, that are mediated by GSK3 activity, or, more specifically, characterized by a need for the inhibition of GSK3.

For example, Klein *et al.*, PNAS 93:8455-9 (1996) report that lithium ion inhibits GSK3 activity. Lithium has been reported to have anti-diabetic effects such as reduction of plasma glucose levels, increased glycogen uptake, potentiation of insulin, and stimulation of glycogen synthesis in skin, muscle, and fat cells. Lithium, however, effects molecular targets other than GSK3, and is, therefore, not a widely accepted therapy for diabetics.

GSK3 is a proline-directed serine/threonine kinase. Other examples of GSK3 mediated diseases or conditions include, without limitation, obesity, various CNS disorders such as Alzheimer's Disease, bipolar disorder, and schizophrenia, neurotraumatic injuries such as acute stroke, immune potentiation, baldness or hair loss, atherosclerotic cardiovascular disease, hypertension, polycystic ovary syndrome, ischemia, brain trauma or injury, Immunodeficiency, and cancer. See, for example, published PCT application WO 00/38675, the background of which is herein incorporated by reference.

In addition other tyrosine kinases, such as TIE, also are implicated by the compounds of the present invention. The acronym TIE represents "tyrosine kinase containing Ig and EGF homology domains." TIE is used to identify a class of receptor tyrosine kinases, which are exclusively expressed in vascular endothelial cells and early hemopoietic cells. Angiopoietin 1 (Ang1), a ligand for the endothelium-specific receptor tyrosine kinase TIE-2, is an angiogenic factor. See, Davis *et al.*, Cell, 1996, 87:1161-1169; Partanen *et al.*, Mol. Cell Biol., 12:1698-1707 (1992); U.S. Patent Nos.

5,521,073; 5,879,672; 5,877,020; and 6,030,831. Ang1 and its receptor TIE-2 function in the later stages of vascular development, i.e., during vascular remodeling (remodeling refers to formation of a vascular lumen) and maturation. See, Yancopoulos et al., Cell, 1998, 93:661-664; Peters, K.G., Circ. Res., 1998, 83(3):342-3; 5 Suri et al., Cell, 87, 1171-1180 (1996). Consequently, inhibition of TIE-2 would be expected to disrupt remodeling and maturation of new vasculature initiated by angiogenesis thereby disrupting the angiogenic process. Thus, inhibition of TIE-2 should prevent tumor angiogenesis and serve to retard or eradicate tumor growth. Accordingly, a treatment for cancer or other disorders associated with inappropriate 10 angiogenesis could be provided.

As used herein, angiogenesis is defined as involving (i) activation of endothelial cells; (ii) increased vascular permeability; (iii) subsequent dissolution of the basement membrane and extravasation of plasma components leading to formation of a provisional fibrin gel extracellular matrix; (iv) proliferation and mobilization of 15 endothelial cells; (v) reorganization of mobilized endothelial cells to form functional capillaries; (vi) capillary loop formation; and (vii) deposition of basement membrane and recruitment of perivascular cells to newly formed vessels. Normal angiogenesis is activated during tissue growth, from embryonic development through maturity, and then enters a period of relative quiescence during adulthood. Normal angiogenesis is 20 also activated during wound healing, and at certain stages of the female reproductive cycle. Inappropriate angiogenesis has been associated with several disease states including various retinopathies; ischemic disease; atherosclerosis; chronic inflammatory disorders; and cancer. The role of angiogenesis in disease states is discussed in Fan et al., Trends in Pharmacol Sci. 16:54-66; Shawver et al., DDI Vol. 2, 25 No. 2 February 1997; Folkmann, 1995, Nature Medicine, 1:27-31.

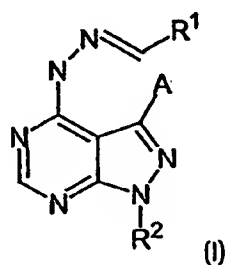
For example, in cancer, the growth of solid tumors has been shown to be angiogenesis dependent. See Folkmann, J., J. Nat'l. Cancer Inst., 1990, 82, 4-6. Consequently, the targeting of pro-angiogenic pathways in cancer treatment is a strategy being widely pursued in order to provide new therapeutics in these areas of 30 great, unmet medical need. The role of tyrosine kinases involved in angiogenesis and in the vascularization of solid tumors may prove useful in the creation of effective medicaments.

5

Thus, the compounds of the present invention are believed useful in a variety of disease states, each of which may be characterized as mediated by inhibition or antagonism of protein kinases.

## 5 SUMMARY OF THE INVENTION

The present invention includes compounds of Formula (I)



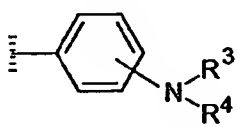
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including salts, solvates, and pharmaceutically acceptable derivatives thereof,

wherein A is H, alkyl, or aryl;

15  $R^1$  is  $D^1$ ,  $D^2$ ,  $D^3$ ,  $D^4$ , or  $D^5$ ,

wherein  $D^1$  is



20 and  $R^3$  and  $R^4$  are each independently H, alkyl, alkylsulfonyl, or  $-C(O)-(CH_2)_x-R^5$ ,

where  $R^5$  is alkyl, acyl, alkoxy,  $-(O)-(CH_2)_x-(O)-$ alkyl, or  $-NR^6R^7$ ,

where  $R^6$  and  $R^7$  are each independently H or alkyl, or

25

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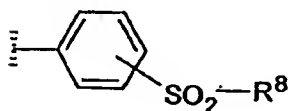
$R^6$  and  $R^7$  combine to form a 5- or 6-membered ring, optionally containing one or more additional heteroatoms, optionally containing one or more degrees of unsaturation, and optionally substituted one or more times with alkyl, hydroxy, carboxy, acyl, alkoxy, or halogen,

5

or  $R^3$  and  $R^4$  combine to form a 5- or 6-membered ring, optionally containing one or more additional heteroatoms, optionally containing one or more degrees of unsaturation, and optionally substituted one or more times with alkyl, hydroxy, carboxy, alkoxy, acyl, or halogen;

10

wherein  $D^2$  is



and  $R^8$  is alkyl, or  $-NR^9R^{10}$ ,

15

where  $R^9$  and  $R^{10}$  are each independently selected from H, alkyl, or  $-(CH_2)_x-NR^6R^7$ ,

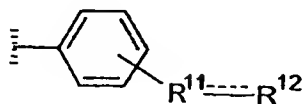
where  $R^6$  and  $R^7$  are each independently H or alkyl,

20

or  $R^6$  and  $R^7$  combine to form a 5- or 6-membered ring, optionally containing one or more additional heteroatoms, optionally containing one or more degrees of unsaturation, and optionally substituted one or more times with alkyl, hydroxy, carboxy, acyl, alkoxy, or halogen;

25

wherein  $D^3$  is



and

7

the dashed line represents an optional double bond;

when  $R^{11}$  is  $-(CH_2)_x$ , the optional dashed double bond does not exist, and  $R^{12}$  is alkylsulfonyl or  $-NR^{13}R^{14}$ ,

5

where  $R^{13}$  and  $R^{14}$  are each independently selected from H, alkyl,  $-(CH_2)_x-R^{17}$ , where  $R^{17}$  is alkoxy or  $-NR^{15}R^{16}$ ,

where  $R^{15}$  and  $R^{16}$  are each independently H or alkyl,

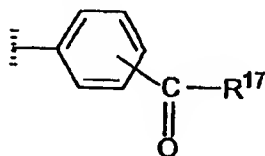
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or  $R^{13}$  and  $R^{14}$  combine to form a 5- or 6-membered ring, optionally containing one or more additional heteroatoms, optionally containing one or more degrees of unsaturation, and optionally substituted one or more times with alkyl or  $-(CH_2)_x-OH$ ;

15

when  $R^{11}$  is  $-(CH)-$ , the optional dashed double bond exists, and  $R^{12}$  is  $-(CH)-C(O)-OH$ ;

wherein  $D^4$  is



20

and  $R^{17}$  is hydroxy, alkoxy, or  $-NR^{18}R^{19}$ ,

where  $R^{18}$  and  $R^{19}$  are each independently selected from H, alkyl,  $-(CH_2)_x-R^{20}$ ,

25

where  $R^{20}$  is alkylsulfonyl, hydroxy, aryl said aryl optionally substituted with hydroxy or alkoxy, heteroaryl, or  $-NR^{21}R^{22}$ ,



where  $R^{21}$  and  $R^{22}$  are each independently selected from H, acyl, alkyl,

or  $R^{21}$  and  $R^{22}$  combine to form a 5- or 6-membered ring, optionally containing one or more additional heteroatoms, optionally containing one or more degrees of unsaturation, and optionally substituted with alkyl or  $-(CH_2)_x-OH$ ;

or  $R^{18}$  and  $R^{19}$  combine to form a 5- or 6-membered ring, optionally containing one or more additional heteroatoms, optionally containing one or more degrees of unsaturation, and optionally substituted with  $-(CH_2)_x-R^{23}$ ,

where  $R^{23}$  is alkoxy, hydroxy,  $-C(O)-R^{24}$ , where  $R^{24}$  is a 5- or 6-membered ring optionally containing one or more heteroatoms and optionally containing one or more degrees of unsaturation, or  $-NR^{25}R^{26}$ , where  $R^{25}$  and  $R^{26}$  are each independently H or alkyl;

wherein  $D^5$  is

a 5- or 6- membered ring, optionally containing one or more heteroatoms, optionally containing one or more degrees of unsaturation, optionally fused with an additional 5- or 6- membered ring that optionally contains one or more heteroatoms and optionally contains one or more degrees of unsaturation,

wherein the ring or fused ring system may be optionally substituted one or more times with halogen, alkyl, haloalkyl, alkylsulfonyl, alkylthio, hydroxy, alkoxy, oxo, sulfonyl, sulfate ion, nitro, cyano, carboxy, alkoxycarbonyl, aryl where said aryl may be optionally substituted with sulfamoyl, heteroaryl where said heteroaryl may be optionally substituted with alkyl, or  $-NR^{27}R^{28}$ ,

where  $R^{27}$  and  $R^{28}$  are each independently H, alkyl, acyl, alkoxy, alkoxy carbonyl, carboxy, or  $-(CH_2)_x-NR^{29}R^{30}$ , where  $R^{29}$  and  $R^{30}$  are each independently selected from H and alkyl,

or  $R^{27}$  and  $R^{28}$  combine to form a 5- or 6- membered ring, optionally containing one or more additional heteroatoms, optionally containing one or more degrees of unsaturation, and optionally substituted one or more times with alkyl, hydroxy, carboxy, acyl, alkoxy, or halogen,

or  $-(O)_y-(CH_2)_x-R^{31}$ , where  $R^{31}$  is hydroxy, alkoxy, haloalkyl, aryl optionally substituted with halogen, or  $-NR^{27}R^{28}$ , where  $R^{27}$  and  $R^{28}$  are as defined above;

wherein for each occurrence, x independently is 0, 1, 2, or 3;

wherein for each occurrence, y independently is 0 or 1; and

$R^2$  is phenyl, substituted one or more times with alkyl, alkoxy, halogen, haloalkyl, haloalkoxy, nitro, or  $-NR^{31}R^{32}$ ,

wherein  $R^{31}$  and  $R^{32}$  are each independently selected from H, alkyl, acyl, or  $-(CH_2)_z-R^{33}$ ,

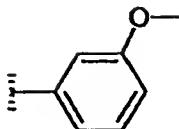
where z is 0, 1, or 2;

and  $R^{33}$  is cycloalkyl.

Preferably  $R^1$  is  $D^5$ . More preferably,  $D^5$  is pyridyl. More preferably  $D^5$  is 4-pyridyl. Preferably  $R^2$  is phenyl substituted with alkoxy. More preferably the alkoxy is methoxy.

10

Preferably R<sup>2</sup> is



Preferably for each occurrence, said alkyl is C<sub>1</sub>-C<sub>6</sub> alkyl.

5 Preferably R<sup>1</sup> is D<sup>3</sup> and R<sup>11</sup> and R<sup>12</sup> combine to form -(CH)=(CH)-C(O)-OH.

In one preferred embodiment, the stereochemical configuration is *cis*.

In another preferred embodiment the stereochemical configuration is *trans*.

Preferably A is H.

In another embodiment, preferably A is alkyl. More preferably, A is C<sub>1-6</sub> alkyl.

10 More preferably A is selected from propyl or isopropyl.

Another aspect of the present invention includes a pharmaceutical composition that includes a therapeutically effective amount of a compound of the present invention.

15 Preferably the pharmaceutical composition further includes one or more pharmaceutically acceptable carrier(s), diluent(s), or excipient(s).

Another aspect of the present invention includes a method of treating a disorder in a mammal, where the disorder is characterized by misregulation of one or more protein kinase through the administration to said mammal a therapeutically effective amount of a compound of the present invention. Preferably, the kinase is a  
20 serine/threonine kinase. More preferably the kinase is GSK3. Alternatively, the kinase may be a tyrosine kinase. In such case, preferably the kinase is TIE2.

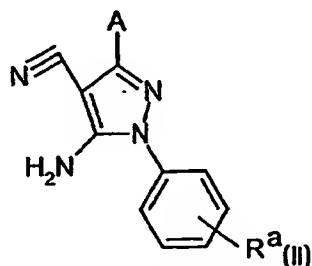
Another aspect of the present invention includes a compound of the present invention for use in therapy. Another aspect includes the use of a compound of the present invention in the preparation of a medicament for use in the treatment of a  
25 disorder characterized by misregulation of one or more protein kinase.

Another aspect of the present invention includes a method of treating type 2 diabetes, hyperlipidemia, obesity, CNS disorders, neurotraumatic injuries, immune potentiation, baldness or hair loss, atherosclerotic cardiovascular disease, hypertension, polycystic ovary syndrome, ischemia, immunodeficiency, and cancer,

through the administration to said mammal of a therapeutically effective amount of a compound of the present invention.

Another aspect of the present invention includes a method of treating type II diabetes, through the administration to said mammal therapeutically of effective amounts of a compound of the present invention and at least one additional anti-diabetic agent.

Another aspect of the present invention includes intermediates such as compounds of Formula (II):



including salts, solvates, and pharmaceutically functional derivatives thereof,

where A is H, alkyl, or aryl;

R<sup>a</sup> is alkyl, alkoxy, halogen, haloalkyl, haloalkoxy, nitro, or -NR<sup>b</sup>R<sup>c</sup>,

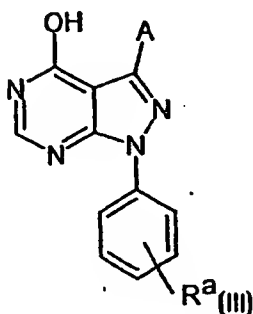
wherein R<sup>b</sup> and R<sup>c</sup> are each independently selected from H, alkyl, acyl, or -(CH<sub>2</sub>)<sub>z</sub>-R<sup>d</sup>,

where z is 0, 1, or 2; and

R<sup>d</sup> is cycloalkyl.

12

Additionally, another aspect of the present invention includes compounds of formula (III)



including salts, solvates, and pharmaceutically functional derivatives thereof,

5

where A is H, alkyl, or aryl;

$R^a$  is alkyl, alkoxy, halogen, haloalkyl, haloalkoxy, nitro, or  $-NR^bR^c$ ,

wherein  $R^b$  and  $R^c$  are each independently selected from H, alkyl, acyl, or  $-(CH_2)_z-$

$R^d$ ,

10

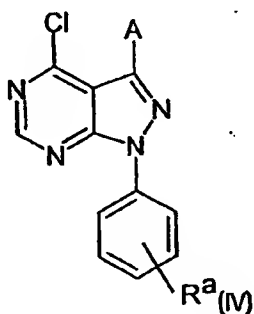
where z is 0, 1, or 2; and

$R^d$  is cycloalkyl.

Additionally, another aspect of the present invention includes compounds of

15

formula (IV)



including salts, solvates, and pharmaceutically functional derivatives thereof,

20

where A is H, alkyl, or aryl;

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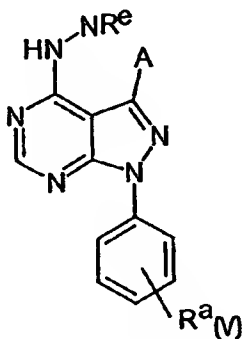
$R^a$  is alkyl, alkoxy, halogen, haloalkyl, haloalkoxy, nitro, or  $-NR^bR^c$ ,

wherein  $R^b$  and  $R^c$  are each independently selected from H, alkyl, acyl, or  $-(CH_2)_z-$   
 $R^d$ ,

5 where  $z$  is 0, 1, or 2; and

$R^d$  is cycloalkyl.

10 Additionally, another aspect of the present invention includes compounds of formula (V)



including salts, solvates, and pharmaceutically functional derivatives thereof,

where  $A$  is H, alkyl, or aryl;

15  $R^a$  is alkyl, alkoxy, halogen, haloalkyl, haloalkoxy, nitro, or  $-NR^bR^c$ ,

wherein  $R^b$  and  $R^c$  are each independently selected from H, alkyl, acyl, or  $-(CH_2)_z-$   
 $R^d$ ,

where  $z$  is 0, 1, or 2;

20

$R^d$  is cycloalkyl; and

$R^c$  is H or  $-C(O)-(O)-C-(CH_3)_3$ .

### DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

The term "alkyl" refers to a straight or branched chain hydrocarbon that may be optionally substituted, with multiple degrees of substitution being allowed. Examples of "alkyl" include, but are not limited to methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, n-pentyl, isobutyl, isopropyl, and the like. The phrase "C<sub>x</sub>-C<sub>y</sub> alkyl" refers to an alkyl group, as defined above, containing the specified number of carbon atoms.

The term "alkylene" refers to a straight or branched chain unsaturated aliphatic hydrocarbon radical that may be optionally substituted, with multiple degrees of substitution being allowed. Examples of "alkylene" include, but are not limited to methylene, ethylene, n-propylene, n-butylene, and the like.

The term "aryl" refers to an optionally substituted benzene ring or to an optionally substituted benzene ring system fused to one or more optionally substituted benzene rings to form, for example, anthracene, phenanthrene, or naphthalene ring systems. Examples of "aryl" groups include, but are not limited to phenyl, 2-naphthyl, 1-naphthyl, biphenyl, as well as substituted derivatives thereof. The term "aralkyl" further refers to groups of -R<sub>a</sub>R<sub>b</sub>, where R<sub>a</sub> is an alkylene as defined herein and R<sub>b</sub> is an aryl as defined herein. Exemplary "aralkyl" groups include C<sub>1</sub>-alkylene-aryl, such as benzyl.

The term "heteroaryl" refers to a monocyclic aromatic ring system, or to a fused bicyclic aromatic ring system comprising two or more aromatic rings. These heteroaryl rings contain one or more nitrogen, sulfur, and/or oxygen atoms, where N-oxides and sulfur oxides and dioxides are permissible heteroatom substitutions and may be optionally substituted, with multiple degrees of substitution being allowed. Examples of "heteroaryl" groups used herein include furan, thiophene, pyrrole, imidazole, pyrazole, triazole, tetrazole, thiazole, oxazole, isoxazole, oxadiazole, thiadiazole, isothiazole, pyridine, pyridazine, pyrazine, pyrimidine, quinoline, isoquinoline, benzofuran, benzothiophene, indole, indazole, and substituted versions thereof. The term "heteroaralkyl" further refers to groups of -R<sub>a</sub>R<sub>b</sub>, where R<sub>a</sub> is an alkylene as defined herein and R<sub>b</sub> is a heteroaryl as defined herein.

As used herein, the term "acyl" refers to the group  $-C(O)R_a$ , where  $R_a$  is H, alkyl, or aryl. Non-limiting examples of "acyl" groups include formyl, acetyl, benzoyl, and the like.

The term "alkoxy" refers to the group  $-OR_a$ , where  $R_a$  is alkyl as defined above.  
5 Non-limiting examples of "alkoxy" groups include methoxy, ethoxy, and the like.

As used herein, the term "oxo" refers to the group  $=O$ .

As used herein, the term "hydroxy" refers to the group  $-OH$ .

As used herein, the term "carboxy" refers to the group  $-COOH$ .

The term "halogen" refers to fluorine, chlorine, bromine, or iodine.

10 The term "haloalkyl" refers to an alkyl group, as defined herein, that is substituted with at least one halogen. Non-limiting examples of "haloalkyl" groups include methyl, ethyl, propyl, isopropyl, n-butyl, and t-butyl substituted independently with one or more halogens, e.g., fluoro, chloro, bromo, and/or iodo. The term "haloalkyl" should be interpreted to include such substituents as perfluoroalkyl and  
15 the like.

The term "haloalkoxy" refers to the group  $-OR_a$ , where  $R_a$  is haloalkyl as defined above.

As used herein, the term "sulfonyl" shall refer to the group  $-S(O)_2-$ .

As used herein, the term "alkylsulfonyl" refers to the group  $-S(O)_2R_a$ , where  $R_a$   
20 is alkyl as defined above.

As used herein, the term "alkylthio" refers to the group  $-SR_a$ , where  $R_a$  is alkyl as defined above.

As used herein, the term "sulfamoyl" refers to a group  $-SO_2-NH_2$ .

As used herein, the term "carbamoyl" refers to the group  $-C(O)NH_2$ .

25 As used herein, the term "carboxamide" refers to the group  $-C(O)N(R_a)_2$ , where  $R_a$  is alkyl or aryl as defined herein.

As used herein, the term "alkoxycarbonyl" refers to the group  $-C(O)OR_a$ , where  $R_a$  is alkyl or aryl as defined herein.

30 The compounds of the present invention may have the ability to crystallize in more than one form, a characteristic known as polymorphism. Such polymorphic forms ("polymorphs") are within the scope of the present invention. Polymorphism generally can occur as a response to changes in temperature or pressure, or both, and



can also result from variations in the crystallization process. Polymorphs can be distinguished by various physical characteristics that are known in the art such as x-ray diffraction patterns, solubility, and melting point.

Certain of the compounds described herein contain one or more chiral centers, or may otherwise be capable of existing as multiple stereoisomers. The scope of the present invention includes mixtures of stereoisomers as well as purified enantiomers, or enantiomerically or diastereomerically enriched mixtures. Also included within the scope of the invention are the individual isomers of the compounds, as well as any wholly or partially equilibrated mixtures thereof. The present invention also covers the individual isomers of the compounds represented by the formulas above as mixtures with isomers thereof in which one or more chiral centers are inverted.

As noted above, the present invention includes salts, solvates, and pharmaceutically functional derivatives of the compounds of the present invention. Salts include addition salts, metal salts, or optionally alkylated ammonium salts. Examples of such salts include hydrochloric, hydrobromic, hydroiodic, phosphoric, sulfuric, trifluoroacetic, trichloroacetic, oxalic, maleic, pyruvic, malonic, succinic, citric, mandelic, benzoic, cinnamic, methane sulphonc, ethane sulphonc, picric, and the like. Further salts include lithium, sodium, potassium, magnesium, and the like. Reference is also made to *Journal of Pharmaceutical Science*, 1997, 66, 2, incorporated herein by reference, as relevant to salts.

As used herein, the term "solvate" refers to a complex of variable stoichiometry formed by a solute or a salt or pharmaceutically functional derivative thereof and a solvent. Such solvents for the purpose of the invention should not interfere with the biological activity of the solute. Examples of solvents include, but are not limited to water, methanol, ethanol, and acetic acid. Preferably the solvent used is a pharmaceutically acceptable solvent. Examples of pharmaceutically acceptable solvents include water, ethanol, and acetic acid.

The term "pharmaceutically functional derivative" refers to any pharmaceutically acceptable derivative of a compound of the present invention, for example, an ester or an amide, which upon administration to a mammal is capable of providing (directly or indirectly) a compound of the present invention or an active metabolite thereof. Such derivatives are recognizable to those skilled in the art,

without undue experimentation. Nevertheless reference is made to the teaching of *Burger's Medicinal Chemistry and Drug Discovery*, 5<sup>th</sup> Edition, Vol 1: Principles and Practice, which is incorporated herein by reference to the extent of teaching pharmaceutically functional derivatives.

5           While it is possible that compounds of the present invention may be administered as the raw chemical, preferably the compounds of the present invention are presented as an active ingredient within a pharmaceutical formulation, as are known in the art. Accordingly, the present invention further includes a pharmaceutical formulation comprising a compound of the present invention, or salt,  
10   solvate, or functional derivative thereof together with one or more pharmaceutically acceptable carriers. Optionally, other therapeutic and/or prophylactic ingredients may be included in the pharmaceutical formulation. For example, the compounds of the present invention may be combined with other agents, such as, without limitation, one or more other anti-diabetic agent such as insulin, alpha glucosidase inhibitors,  
15   biguanides, insulin secretagogues such as sulphonylureas, insulin sensitizers such as thiazolidinediones, and/or dipeptidyl peptidase inhibitors.

Formulations of the present invention include those especially formulated for oral, buccal, parental, transdermal, inhalation, intranasal, transmucosal, implant, or rectal administration. Among the variety of administrations, oral administration  
20   typically is preferred. For oral administration tablets, capsules, and caplets may contain conventional excipients such as binding agents, fillers, lubricants, disintegrants, and/or wetting agents. Non-limiting examples of binding agents include syrup, acacia, gelatin, sorbitol, tragacanth, mucilage of starch, or polyvinylpyrrolidone (PVP). Non-limiting examples of fillers include, for example,  
25   lactose, sugar, microcrystalline cellulose, maize-starch, calcium phosphate or sorbitol. Non-limiting examples of lubricants include, for example, magnesium stearate, stearic acid, talc, polyethylene glycol or silica. Non-limiting examples of disintegrants include, for example, potato starch or sodium starch glycollate. A non-limiting example of a wetting agent includes sodium lauryl sulfate. The tablets additionally  
30   may be coated according to methods known in the art.

Alternatively, the compounds of the present invention may be incorporated into oral liquid preparations such as aqueous or oily suspensions, solutions, emulsions,

5 syrups, or elixirs. Moreover, formulations containing these compounds may be presented as a dry product for constitution with water or other suitable vehicle before use. Liquid preparations may contain conventional additives. Non-limiting examples of such additives include suspending agents such as sorbitol syrup, methyl cellulose, glucose/sugar syrup, gelatin, hydroxyethylcellulose, carboxymethyl cellulose, aluminum stearate gel or hydrogenated edible fats. Additionally, emulsifying agents such as lecithin, sorbitan mono-oleate or acacia; non-aqueous vehicles (which may include edible oils) such as almond oil, fractionated coconut oil, oily esters, propylene glycol or ethyl alcohol may be included. Further, preservatives such as methyl or propyl p-hydroxybenzoates or sorbic acid, may be incorporated into the preparation. Such preparations may also be formulated as suppositories, for example, containing conventional suppository bases such as cocoa butter or other glycerides.

10 Additionally, formulations of the present invention may be formulated for parenteral administration by injection or continuous infusion. Formulations for injection may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, for example, sterile, pyrogen-free water, before use.

20 The formulations according to the invention may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation, for example, subcutaneously or intramuscularly, or by intramuscular injection. Accordingly, the compounds of the invention may be formulated with suitable polymeric or hydrophobic materials, such as an emulsion in an acceptable oil, ion exchange resins, or as sparingly soluble derivatives, such as a sparingly soluble salt.

25 Pharmaceutical formulations may be presented in unit dose forms containing a predetermined amount of active ingredient per unit dose. Such a unit may contain certain amounts of a compound of the present invention depending on the condition being treated, the route of administration, and the age, weight and condition of the patient. Preferred unit dosage formulations are those containing a predetermined dose, such as a daily dose, or an appropriate fraction thereof, of an active ingredient.

Such pharmaceutical formulations may be prepared by any of the methods well known in the pharmacy art.

As used herein, the term "effective amount" means that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal, or human that is being sought, for instance, by a researcher or clinician. Furthermore, the term "therapeutically effective amount" means any amount which, as compared to a corresponding subject who has not received such amount, results in improved treatment, healing, prevention, or amelioration of a disease, disorder, or side effect, or a decrease in the rate of advancement of a disease or disorder. The term also includes within its scope amounts effective to enhance normal physiological function.

A "therapeutically effective amount" of a compound of the present invention will depend upon a number of factors including, for example, the age and weight of the animal, the precise condition requiring treatment and its severity, the nature of the formulation, and the route of administration. Therapeutic effectiveness ultimately will be at the discretion of the attendant physician or veterinarian. An effective amount of a salt or solvate, or pharmaceutically functional derivative thereof, may be determined as a proportion of the effective amount of a compound of the present invention *per se*.

## 20 EXPERIMENTALS

The following examples illustrate aspects of this invention, but should not be construed as limitations. Unless otherwise noted, all starting materials were obtained from commercial suppliers or obtained through synthetic methods known to those skilled in the art. As used herein the symbols and conventions used in these processes, schemes and examples are consistent with those used in the contemporary scientific literature, for example, the *Journal of the American Chemical Society* or the *Journal of Biological Chemistry*. Specifically, the following abbreviations may be used in the examples and throughout the specification:

30	g (grams);	mg (milligrams);
	L (liters);	mL (milliliters);
	$\mu$ L (microliters);	psi (pounds per square inch);
	M (molar);	mM (millimolar);

	i. v. (intravenous);	Hz (Hertz);
	MHz (megahertz);	mol (moles);
	mmol (millimoles);	RT (room temperature);
	min (minutes);	h (hours);
5	mp (melting point);	TLC (thin layer chromatography);
	T <sub>r</sub> (retention time);	RP (reverse phase);
	MeOH (methanol);	<i>i</i> -PrOH (isopropanol);
	TEA (triethylamine);	TFA (trifluoroacetic acid);
	TFAA (trifluoroacetic anhydride);	THF (tetrahydrofuran);
10	DMSO (dimethylsulfoxide);	EtOAc (ethyl acetate);
	DCE (dichloroethane);	DMF ( <i>N,N</i> -dimethylformamide);
	HOAc (acetic acid);	EDC (ethylcarbodiimide hydrochloride);
	mCPBA (meta-chloroperbenzoic acid);	
	BOC ( <i>tert</i> -butoxycarbonyl);	CBZ (benzyloxycarbonyl);
15	DCC (dicyclohexylcarbodiimide);	Me (methyl);
	Ac (acetyl);	atm (atmosphere);
	TMSE (2-(trimethylsilyl)ethyl);	TMS (trimethylsilyl);
	TIPS (triisopropylsilyl);	T BS ( <i>t</i> -butyldimethylsilyl);
	DMAP (4-dimethylaminopyridine);	
20	HPLC (high pressure liquid chromatography);	
	Et (ethyl);	<i>t</i> Bu (tert-butyl).

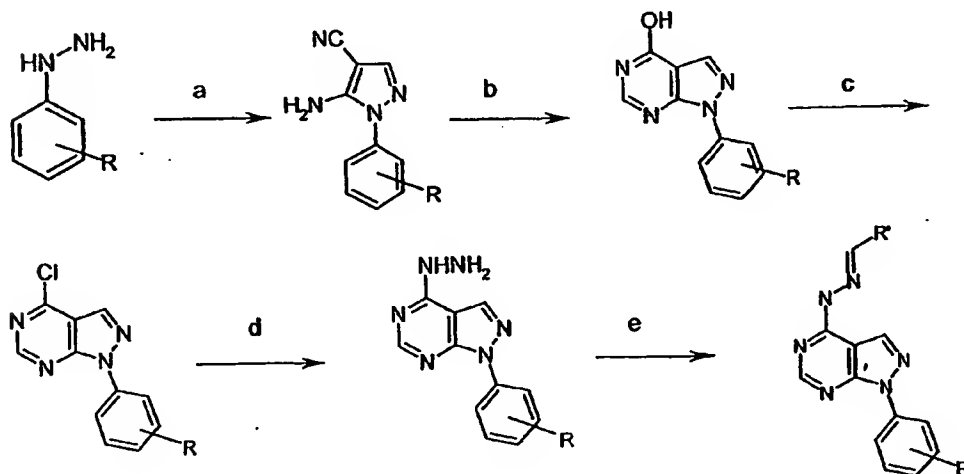
All references to ether are to diethyl ether; brine refers to a saturated aqueous solution of NaCl. Unless otherwise indicated, all temperatures are expressed in °C (degrees Centigrade). All reactions were conducted under an inert atmosphere at room temperature unless otherwise noted.

<sup>1</sup>H NMR spectra were recorded on a Varian VXR-300, a Varian Unity-300, a Varian Unity-400 instrument, or a General Electric QE-300. Chemical shifts are expressed in parts per million (ppm, δ units). Coupling constants are in units of hertz (Hz). Splitting patterns describe apparent multiplicities and are designated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad).

Low-resolution mass spectra (MS) were recorded on a JOEL JMS-AX505HA, JOEL SX-102, or a SCIEX-APIIII spectrometer; high resolution MS were obtained using a JOEL SX-102A spectrometer. All mass spectra were taken under electrospray ionization (ESI), chemical ionization (CI), electron impact (EI) or by fast atom bombardment (FAB) methods. Infrared (IR) spectra were obtained on a Nicolet 510 FT-IR spectrometer using a 1-mm NaCl cell. All reactions were monitored by thin-layer chromatography on 0.25 mm E. Merck silica gel plates (60F-254), visualized with UV light, 5% ethanolic phosphomolybdic acid or p-anisaldehyde solution. Flash column chromatography was performed on silica gel (230-400 mesh, Merck). Optical rotations were obtained using a Perkin Elmer Model 241 Polarimeter. Melting points were determined using a Mel-Temp II apparatus and are uncorrected.

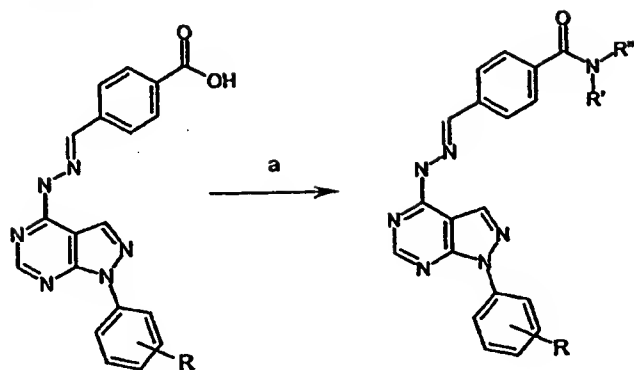
IUPAC names are included to further identify particular compounds of the present invention. The IUPAC names stated herein should in no way limit the scope of the present invention.

Scheme 1:



- a: ethoxymethylenemalonitrile (1 eq), triethylamine (1.2 eq), ethanol; b: formic acid; c: phosphorus oxychloride; d: hydrazine hydrate (6 eq), ethanol; e: appropriate aldehyde (1 eq), pyrrolidine (cat.), ethanol.

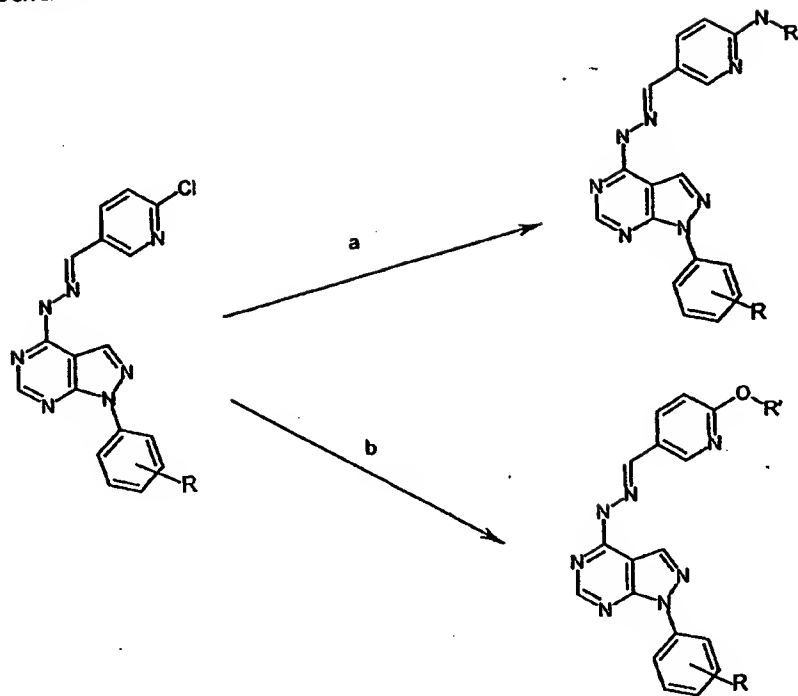
Scheme 2:



a: appropriate amine (1.5 eq), diethylcyanophosphonate (2 eq), triethylamine (3 eq),

5 DMF

Scheme 3:



a: appropriate amine, diisopropylethylamine. b: i: Sodium hydride (12 eq), appropriate alcohol (18 eq), THF ii: DMSO

5

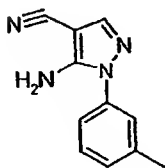
### EXAMPLES

#### Intermediates Example A

#### 4-Hydrazino-1-(3-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidine

10

a. 5-Amino-1-(3-methylphenyl)-1H-pyrazole-4-carbonitrile



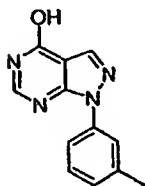


- To 1-(3-methylphenyl)hydrazine hydrochloride (2.00 g, 12.61 mmol) in 25 mL of ethanol was added 2-(ethoxymethylene)malononitrile (1.54 g, 12.61 mmol) and triethylamine (2.3 mL, 16.39 mmol). Mixture was refluxed for ca. 3 h, concentrated under reduced pressure and the residue was partitioned between saturated aqueous sodium bicarbonate and ethyl acetate. The product was isolated by flash chromatography as a white solid (1.135 g, 45%).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.63 (s, 1H), 7.40 (t, 1H), 7.26 (m, 3H), 4.58 (s, 2H), 2.42 (s, 3H) ppm.

10

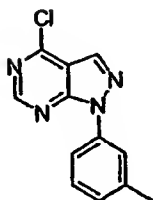
- b. 1-(3-Methylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-ol



- 15 5-Amino-1-(3-methylphenyl)-1*H*-pyrazole-4-carbonitrile (a, above) (1.13 g, 5.71 mmol) was dissolved in 50 mL of formic acid and reflux for ca. 24 h. The mixture as cooled to RT and diluted with ether. The resulting solid were collected by filtration and washed with ether to give the product as a white solid (0.99 g, 77%).

- 20 <sup>1</sup>H NMR (DMSO) δ 12.44 (s, 1H), 8.31 (s, 1H), 8.20 (d, 1H), 7.85 (s, 1H), 7.82 (d, 1H), 7.43 (t, 1H), 7.21 (d, 1H), 2.39 (s, 3H) ppm.

c 4-Chloro-1-(3-methylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine

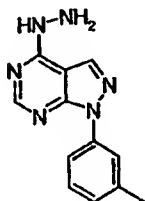


5 1-(3-Methylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-ol (b, above) (0.98 g, 4.32 mmol) was dissolved in phosphorous oxychloride (5 mL) and 2-3 drops of DMF was added. The mixture was heated at reflux for ca. 3.5 h. The mixture was concentrated under reduced pressure, quenched into an ice/sodium bicarbonate mixture and extracted with methylene chloride. The organic phase was washed with aqueous sodium  
10 bicarbonate and concentrated to give the product as a white solid (0.95 g, 90%).

<sup>1</sup>H NMR (DMSO)  $\delta$  8.98 (s, 1H), 8.75 (s, 1H), 7.95 (s, 1H), 7.93 (d, 1H), 7.48 (t, 1H), 7.25 (d, 1H), 2.42 (s, 3H) ppm. ES-MS  $m/z$  245 (MH<sup>+</sup>).

15

d. 4-Hydrazino-1-(3-methylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine



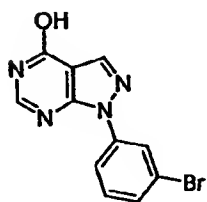
4-Chloro-1-(3-methylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (c, above) (0.50 g, 2.05  
20 mmol) was dissolved in ethanol (25 mL) and hydrazine mono-hydrate (0.60 mL, 12.3 mmol) was added. The mixture was heated at 45 C for ca. 18 h and concentrated under reduced pressure. The resulting solid was triturated with aqueous sodium bicarbonate to give the product as a white solid (0.45 g, 91%).

ES-MS  $m/z$  241 ( $MH^+$ ).

Intermediates Example B

5 1-(3-Bromophenyl)-4-chloro-1H-pyrazolo[3,4-d]pyrimidine.

a. 1-(3-Bromophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ol.



10

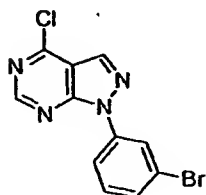
A solution of 5-amino-1-(3-bromophenyl)-1H-pyrazole-4-carbonitrile (1.47 g, 5.59 mmol) in 50 mL of 88% formic acid was heated to 100°C for 18 hours. The reaction mixture was cooled to room temperature and diluted with diethyl ether. The precipitated solid was collected by filtration, washed with ether and dried under vacuum to give 1.37 g (84%) of product as a white solid.

15

$^1H$  NMR (DMSO)  $\delta$  12.50 (br s, 1H), 8.35 (m, 2H), 8.25 (m, 1H), 8.10 (m, 1H), 7.60 (m, 1H), 7.50 (t, 1H) ppm. ES-MS  $m/z$  291 ( $M+2$ ) $^+$

20

b. 1-(3-Bromophenyl)-4-chloro-1H-pyrazolo[3,4-d]pyrimidine



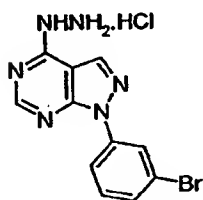
A suspension of 1-(3-bromophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-ol (a, above) (1.36 g, 4.67 mmol) in 5 mL of phosphorus oxychloride was heated to 100°C for 4 hours.

- 5 The reaction mixture was cooled to room temperature, poured into ice and extracted with ethyl acetate. The organic phase was washed with saturated aqueous sodium bicarbonate and dried over anhydrous sodium sulfate. The solvent was evaporated under vacuum to give 0.84 g (58%) of product as a white solid.

- 10 <sup>1</sup>H NMR (DMSO) δ 9.05 (s, 1H), 8.80 (s, 1H), 8.45 (m, 1H) 8.20 (d, 1H), 7.45 (d, 1H), 7.40 (t, 1H).

c. 1-(3-Bromophenyl)-4-hydrazino-1*H*-pyrazolo[3,4-*d*]pyrimidine hydrochloride

15



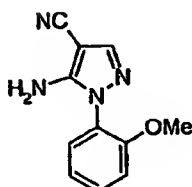
- Hydrazine hydrate (0.094 mL, 1.93 mmol) was added to a solution of 1-(3-bromophenyl)-4-chloro-1*H*-pyrazolo[3,4-*d*]pyrimidine (b, above) in 5 mL of absolute ethanol. The mixture was heated at reflux overnight, cooled to room temperature and the solvent evaporated to give 0.095 g of product as a white solid.
- 20

ES-MS *m/z* 307 (*M*+2), 308.

25

#### Intermediates Example C

4-Hydrazino-1-(2-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine

a. 5-Amino-1-(2-methoxyphenyl)-1*H*-pyrazole-4-carbonitrile

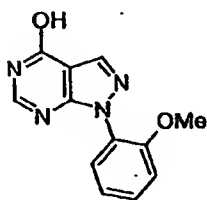
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2-Methoxyphenylhydrazine hydrochloride (1.00 g, 5.70 mmol) was treated with ethoxymethylenemalononitrile (0.698 g, 5.70 mmol) and triethylamine (0.95 mL, 6.80 mmol) as described for 5-amino-1-(3-methylphenyl)-1*H*-pyrazole-4-carbonitrile (Intermediates Example A) to give 0.46 g (38%) of product as an off-white solid.

10

<sup>1</sup>H NMR (DMSO) δ 7.65 (s, 1H), 7.45 (t, 1H), 7.25 (d, 1H), 7.20 (d, 1H), 7.05 (t, 1H), 6.35 (br s, 2H), 3.80 (s, 3H) ppm.

15

b. 1-(2-Methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-ol.

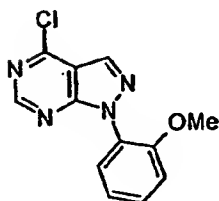
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5-Amino-1-(2-methoxyphenyl)-1*H*-pyrazole-4-carbonitrile (a, above) (0.43 g, 2.01 mmol) was treated with 88% formic acid as described for 1-(3-methylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-ol (Intermediates Example A) to give 0.302 g (62%) of product as an off-white solid.

<sup>1</sup>H NMR (DMSO) δ 12.25 (br s, 1H), 8.25 (s, 1H), 8.00 (s, 1H), 7.50 (m, 1H), 7.40 (m, 1H), 7.30 (m, 1H), 7.10 (m, 1H), 3.75 (s, 3H) ppm. ES-MS m/z 243 (MH<sup>+</sup>).

c. 4-Chloro-1-(2-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine.

5

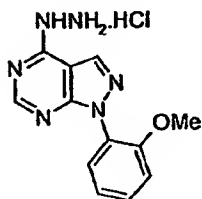


10 1-(2-Methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-ol (b, above) (0.296 g, 1.22 mmol) was treated with phosphorus oxychloride as described for 4-chloro-1-(3-methylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (Intermediates Example A) to give 0.230 (72%) of product as a white solid.

15 <sup>1</sup>H NMR (DMSO) δ 8.85 (s, 1H), 8.70 (s, 1H), 7.60 (t, 1H), 7.50 (d, 1H), 7.30 (d, 1H), 7.10 (t, 1H), 3.70 (s, 3H) ppm.

d. 4-Hydrazino-1-(2-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine.

20



4-Chloro-1-(2-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (c, above) (0.228 g, 0.87 mmol) was treated with hydrazine hydrate (0.25 mL, 5.25 mmol) as described for 4-hydrazino-1-(3-methylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (Intermediates Example A) to give 0.349g of product as an off-white solid.

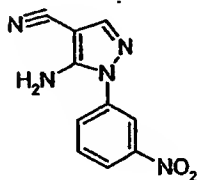
5

ES-MS *m/z* 256 (MH<sup>+</sup>)

Intermediates Example D

10 4-Hydrazino-1-(3-nitrophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine

a. 5-Amino-1-(3-nitrophenyl)-1*H*-pyrazole-4-carbonitrile

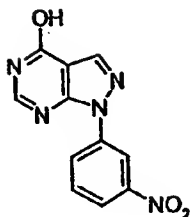


15

To 2-1-(3-nitrophenyl)hydrazine hydrochloride (3.00 g, 15.82 mmol) in 40 mL of ethanol was added 2-(ethoxymethylene)malononitrile (1.93 g, 15.82 mmol) and triethylamine (2.9 mL, 20.6 mmol). Mixture was refluxed of ca. 6 h. After cooling to RT the resulting solids were collected to give the product as a yellow solid (2.15 g, 59 %).

20

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.47 (t, 1H), 8.31 (dd, 1H), 7.95 (d, 1H), 7.76 (t, 1H), 7.71 (s, 1H), 4.66 (s, 2H) ppm.

b. 1-(3-Nitrophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-ol

5

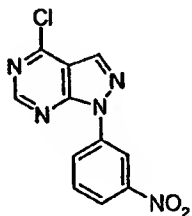
5-Amino-1-(3-nitrophenyl)-1*H*-pyrazole-4-carbonitrile (a, above) (2.00 g, 8.73 mmol) was dissolved in 40 mL of formic acid and refluxed for ca. 30 h. The mixture was cooled to RT and diluted with ether. The resulting solid was collected by filtration and washed with ether to give the product as a white solid (2.10 g, 100 %).

10

<sup>1</sup>H NMR (DMSO):  $\delta$  12.62 (s, 1H), 9.03 (t, 1H), 8.57 (dd, 1H), 8.43 (s, 1H), 8.32 (s, 1H), 8.23 (dd, 1H), 7.87 (t, 1H) ppm.

c. 4-Chloro-1-(3-nitrophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine

15



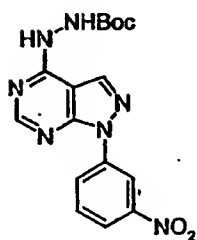
1-(3-Nitrophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-ol (b, above) (2.1 g, 8.73 mmol) was dissolved in phosphorous oxychloride (25 mL) and 2-3 drops of DMF was added. The mixture was heated at reflux for ca. 5 h. The mixture was concentrated under reduced pressure, quenched into an ice sodium bicarbonate mixture and extracted with methylene chloride. The organic phase was washed with aqueous sodium bicarbonate and concentrated to give the product as a white solid (2.1 g, 87%).

20



<sup>1</sup>H NMR (DMSO) δ 9.11 (t, 1H), 9.09 (s, 1H), 8.88 (s, 1H), 8.66 (dd, 1H), 8.28 (dd, 1H), 7.93 (t, 1H) ppm.

- 5 d. *tert*-Butyl 2-[1-(3-nitrophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazinecarboxylate

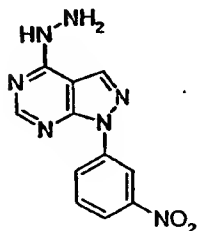


- 10 4-Chloro-1-(3-nitrophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (c, above) (1.00 g, 3.63 mmol) and *tert*-butyl hydrazinecarboxylate (0.58 g, 4.35 mmol) were dissolved in ethanol (200 mL). Triethylamine (0.76 mL, 5.44 mmol) was added. The mixture was refluxed for ca. 18 h and concentrated under reduced pressure. The residue as partitioned between methylene chloride and aqueous sodium bicarbonate to give the product as a white solid (1.2 g, 89%).
- 15

ES-MS *m/z* 372 (MH<sup>+</sup>).

- e. 4-Hydrazino-1-(3-nitrophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine

20



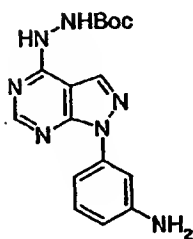
*tert*-Butyl 2-[1-(3-nitrophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazinecarboxylate (d, above) (0.60 g, 1.6 mmol) was dissolved in methylene chloride (50 mL) and trifluoroacetic acid (15 mL). The mixture was stirred at RT for 1 h. The solvent was removed under reduced pressure and the residue was dissolved in methylene chloride (50 mL) and 4N hydrochloric acid in dioxane (8 mL). The solvent was removed under reduced pressure to give the product as the hydrochloride salt (0.62 g, 98%).

ES-MS  $m/z$  272 ( $MH^+$ ).

#### Intermediates Example E

##### *N*-[3-(4-Hydrazino-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)phenyl]acetamide

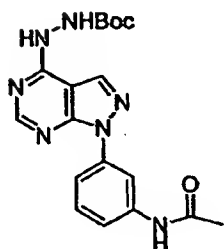
a. *tert*-Butyl 2-[1-(3-aminophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazinecarboxylate



To *tert*-butyl 2-[1-(3-nitrophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazinecarboxylate (Intermediates Example D) (0.70 g, 1.89 mmol) in ethanol (150 mL) was added palladium on carbon (10 %, 0.6 g). The mixture was stirred under 1 atm of hydrogen for 3 h. The mixture was flushed with nitrogen, filtered and concentrated to give the product as a white foam (0.67 g, 99%).

ES-MS  $m/z$  342 ( $MH^+$ ).

- b. *tert*-Butyl 2-{1-[3-(acetylamino)phenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl}hydrazinecarboxylate



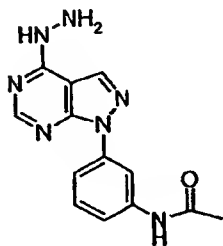
To *tert*-butyl 2-[1-(3-aminophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazinecarboxylate (a, above) (100 mg, 0.29 mmol) in THF (8 mL) was added triethylamine (0.51 mL, 0.37 mmol) and acetyl chloride (0.021 mL, 0.29 mmol). The mixture was stirred at RT for 40 min. and then partitioned between ethyl acetate and aqueous sodium bicarbonate to give the product as a white solid (110 mg, 100%).

10

ES-MS  $m/z$  382 ( $MH^+$ ).

15

- c. *N*-[3-(4-Hydrazino-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)phenyl]acetamide



*tert*-Butyl 2-{1-[3-(acetylamino)phenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl}hydrazinecarboxylate (b, above) (0.10 g, 0.27 mmol) was dissolved in methylene chloride (20 mL) and trifluoroacetic acid (10 mL). The mixture was stirred at RT for 1 h.

35

The solvent was removed under reduced pressure and the residue as dissolve in methylene chloride (20 mL) and 4N hydrochloric acid in dioxane (5 mL). The solvent was removed under reduced pressure to give the product as the hydrochloride salt (0.82 g, 95%).

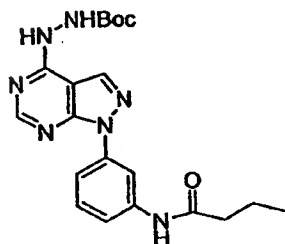
5

ES-MS  $m/z$  284 ( $MH^+$ ).

#### Intermediates Example F

10 *N*-[3-(4-Hydrazino-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)phenyl]butanamide

- a. *tert*-butyl 2-{1-[3-(butylamino)phenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl}hydrazinecarboxylate



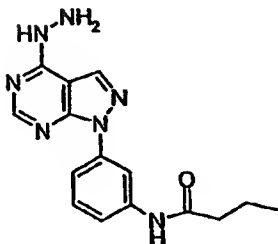
15

To *tert*-butyl 2-[1-(3-aminophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazinecarboxylate (Intermediates Example E) (100 mg, 0.29 mmol) in THF (8 mL) was added triethylamine (0.51 mL, 0.37 mmol) and butyryl chloride (31 mg, 0.29 mmol). The mixture was stirred at RT for 1 h and then partitioned between ethyl acetate and aqueous sodium bicarbonate to give the product as a clear solid (120 mg, 100%).

20

ES-MS  $m/z$  410 ( $MH^+$ ).

25

b. *N*-[3-(4-Hydrazino-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)phenyl]butanamide

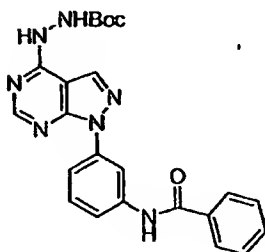
- tert-Butyl 2-{1-[3-(butyrylamino)phenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl}hydrazinecarboxylate (a, above) (0.12 g, 0.29 mmol) was dissolved in methylene chloride (20 mL) and trifluoroacetic acid (8 mL). The mixture was stirred at RT for 1h. The solvent was removed under reduced pressure and the residue was dissolved in methylene chloride (20 mL) and 4N hydrochloric acid in dioxane (4 mL). The solvent was removed under reduced pressure to give the product as the hydrochloride salt (0.10 g, 100%).

ES-MS *m/z* 312 (MH<sup>+</sup>).

15 Intermediates Example G*N*-[3-(4-Hydrazino-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)phenyl]benzamide

- a. *tert*-Butyl 2-{1-[3-(benzoylamino)phenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl}hydrazinecarboxylate

20

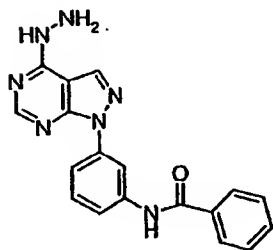


To *tert*-butyl 2-[1-(3-aminophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazinecarboxylate (Intermediates Example E) (100 mg, 0.29 mmol) in THF (8 mL) was added triethylamine (0.51 mL, 0.37 mmol) and benzoyl chloride (41 mg, 0.29 mmol). The mixture was stirred at RT for 3 days and then partitioned between ethyl acetate and aqueous sodium bicarbonate to give the crude product as a white solid.  
5 The product was purified by silica gel chromatography (2:1 ethyl acetate:hexanes) to give the product as a white solid (82 mg, 64%).

ES-MS  $m/z$  444(MH<sup>+</sup>).

10

b. *N*-[3-(4-Hydrazino-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)phenyl]benzamide



15 *tert*-Butyl 2-[1-[3-(benzoylamino)phenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazinecarboxylate (a, above) (0.75 g, 0.17 mmol) was dissolved in methylene chloride (10 mL) and trifluoroacetic acid (8 mL). The mixture was stirred at RT for 1h. The solvent was removed under reduced pressure and the residue was dissolved in methylene chloride (10 mL) and 4N hydrochloric acid in dioxane (4 mL). The solvent  
20 was removed under reduced pressure to give the product as the hydrochloride salt (0.65 g, 100%).

ES-MS  $m/z$  346 (MH<sup>+</sup>).

25

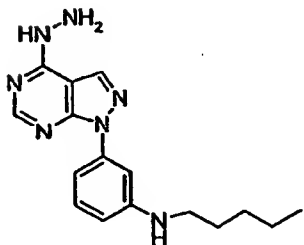
Intermediates Example H3-(4-Hydrazino-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-*N*-pentylaniline

- 5 a. *tert*-Butyl 2-{1-[3-(pentylamino)phenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl}hydrazinecarboxylate



- To *tert*-butyl 2-[1-(3-aminophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazinecarboxylate (Intermediates Example E) (150 mg, 0.44 mmol) in methanol (7 mL) was added pentanal (45 mg, 0.53 mmol). The mixture was stirred at RT for ca. 30 min and resin bound cyanoborohydride (300 mg, approx. 1.0 mmol) was added. The resulting mixture was stirred at RT for ca. 18 h. The mixture was filtered and partitioned between methylene chloride and aqueous sodium bicarbonate to give the crude product. The crude product was purified by silica gel chromatography (1:3 ethyl acetate:hexanes) to give the product (55 mg, 30 %).

ES-MS  $m/z$  412 ( $MH^+$ ).

b. 3-(4-Hydrazino-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-*N*-pentylaniline

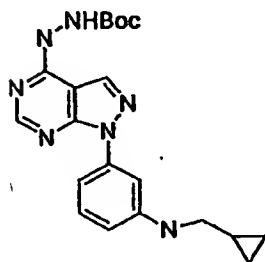
- 5 *tert*-Butyl 2-{1-[3-(pentylamino)phenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl}hydrazinecarboxylate (a, above) (50 mg, 0.12 mmol) was dissolved in methylene chloride (5 mL) and trifluoroacetic acid (5 mL). The mixture was stirred at RT for 1.5h. The solvent was removed under reduced pressure and the residue was dissolved in methylene chloride (5 mL) and 1N hydrochloric acid in diethyl ether (5 mL). The solvent was removed under reduced pressure to give the product as the hydrochloride
- 10 salt (0.42 g, 100%).

ES-MS *m/z* 312 (*MH*<sup>+</sup>).



Intermediates Example I*N*-(Cyclopropylmethyl)-3-(4-hydrazino-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)aniline

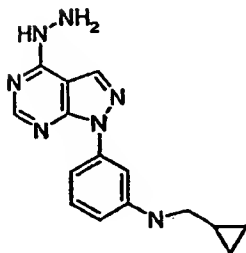
- 5 a. *tert*-Butyl 2-[1-{3-[(cyclopropylmethyl)amino]phenyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazinecarboxylate



- To *tert*-butyl 2-[1-(3-aminophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazinecarboxylate (Intermediates Example E) (150 mg, 0.44 mmol) in methanol (6 mL) was added sodium acetate (ca. 20 mg) and cyclopropanecarbaldehyde (39 mg, 0.55 mmol). The mixture was stirred at RT for ca. 1 h and resin bound cyanoborohydride (500 mg, approx. 1.7 mmol) was added. The resulting mixture was stirred at RT for ca. 6 h. The mixture was filtered and partitioned between methylene chloride and aqueous sodium bicarbonate to give the crude product. The crude product was purified by silica gel chromatography (1:3 ethyl acetate:hexanes) to give the product (60 mg, 35 %).

ES-MS *m/z* 396 (MH<sup>+</sup>).

- b. *N*-(Cyclopropylmethyl)-3-(4-hydrazino-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)aniline



5

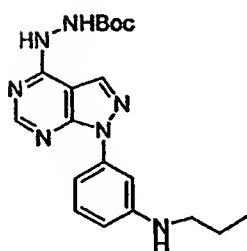
*tert*-Butyl 2-(1-{3-[(cyclopropylmethyl)amino]phenyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)hydrazinecarboxylate (a, above) (57 mg, 0.14 mmol) was dissolved in methylene chloride (8 mL) and trifluoroacetic acid (6 mL). The mixture was stirred at RT for 1.5h. The solvent was removed under reduced pressure and the residue was dissolved in methylene chloride (8 mL) and 4N hydrochloric acid in dioxane (4 mL). The solvent was removed under reduced pressure to give the product as the hydrochloride salt (48 mg, 100%).

15

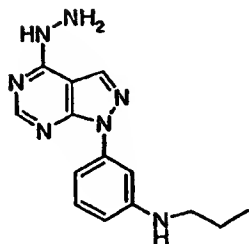
ES-MS  $m/z$  296 ( $MH^+$ ).

Intermediates Example J3-(4-Hydrazino-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-*N*-propylaniline

- 5 a. *tert*-Butyl 2-{1-[3-(propylamino)phenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl}hydrazinecarboxylate



- 10 To *tert*-butyl 2-[1-(3-aminophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazinecarboxylate (Intermediates Example E) (150 mg, 0.44 mmol) in methanol (6 mL) was added sodium acetate (ca. 20 mg) and propionaldehyde (39 mg, 0.55 mmol). The mixture was stirred at RT for ca. 1 h and resin bound cyanoborohydride (500 mg, approx. 1.7 mmol) was added. The resulting mixture was stirred at RT for ca.
- 15 6 h. The mixture was filtered and partitioned between methylene chloride and aqueous sodium bicarbonate to give the crude product. The crude product was purified by silica gel chromatography (1:3 ethyl acetate:hexanes) to give the product (65 mg, 39 %).
- 20 ES-MS *m/z* 384 (MH<sup>+</sup>).

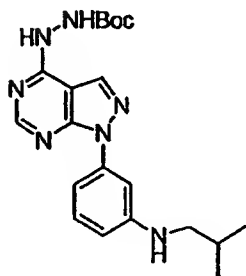
b. 3-(4-Hydrazino-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-*N*-propylaniline

- 5 *tert*-Butyl 2-{1-[3-(propylamino)phenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl}hydrazinecarboxylate (a, above) (60 mg, 0.16 mmol) was dissolved in methylene chloride (8 mL) and trifluoroacetic acid (6 mL). The mixture was stirred at RT for 1.5h. The solvent was removed under reduced pressure and the residue was dissolved in methylene chloride (8 mL) and 4N hydrochloric acid in dioxane (4 mL). The solvent was  
10 removed under reduced pressure to give the product as the hydrochloride salt (51 mg, 100%).

ES-MS  $m/z$  284 ( $MH^+$ ).

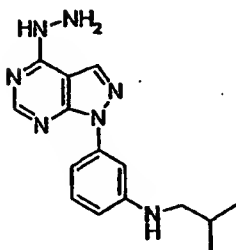
Intermediates Example K3-(4-Hydrazino-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-*N*-isobutylaniline

- 5 a. *tert*-Butyl 2-{1-[3-(isobutylamino)phenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl}hydrazinecarboxylate



- To *tert*-butyl 2-[1-(3-aminophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazinecarboxylate (Intermediates Example E) (150 mg, 0.44 mmol) in methylene chloride (12 mL) was added 2-methylpropanal (48 mg, 0.66 mmol). The mixture was stirred at RT for ca. 1.5 h and sodium triacetoxyborohydride (0.28 g, 1.32 mmol) was added. The resulting mixture was stirred at RT for ca. 2 days. The mixture was partitioned between methylene chloride and aqueous sodium bicarbonate to give the crude product. The crude product was purified by silica gel chromatography (1:3 ethyl acetate:hexanes) to give the product (76 mg, 44 %).

ES-MS  $m/z$  398 ( $MH^+$ ).

b. 3-(4-Hydrazino-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-*N*-isobutylaniline

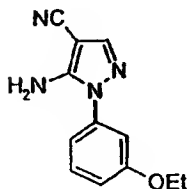
- 5 *tert*-Butyl 2-{1-[3-(isobutylamino)phenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl}hydrazinecarboxylate (a, above) (72 mg, 0.18 mmol) was dissolved in methylene chloride (8 mL) and trifluoroacetic acid (6 mL). The mixture was stirred at RT for 1.5h. The solvent was removed under reduced pressure and the residue was dissolved in methylene chloride (8 mL) and 4N hydrochloric acid in dioxane (4 mL). The solvent was removed under reduced pressure to give the product as the hydrochloride salt (60 mg, 100%).

ES-MS *m/z* 298 (MH<sup>+</sup>).

15

Intermediates Example L1-(3-Ethoxyphenyl)-4-hydrazino-1*H*-pyrazolo[3,4-*d*]pyrimidine

- 20 a. 5-Amino-1-(3-ethoxyphenyl)-1
- H*
- pyrazole-4-carbonitrile

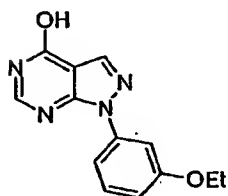


Ethoxymethylenemalononitrile (1.12 g, 9.21 mmol) was added to a solution of 3-ethoxyphenylhydrazine (1.40 g, 9.21 mmol) in 50 mL of absolute ethanol. The mixture was heated at reflux for 1 hour. A crystalline solid formed upon cooling to room temperature. The mixture was refrigerated overnight, filtered, and the crystals washed with hexane and dried under vacuum to give 1.20 g (57%) of pure product.

<sup>1</sup>H NMR (DMSO) δ 7.75 (s, 1H), 7.40 (t, 1H), 7.02 (d, 1H), 6.98 (m, 1H), 6.95 (dd, 1H), 6.65 (br s, 2H), 4.05 (q, 2H), 1.30 (t, 3H) ppm; ES-MS m/z 360 (MH<sup>+</sup>).

10

b. 1-(3-Ethoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-ol.

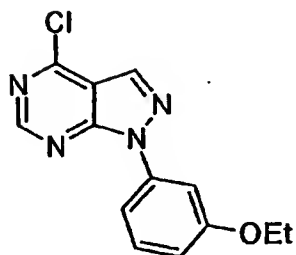


15

A solution of 5-amino-1-(3-ethoxyphenyl)-1*H*-pyrazole-4-carbonitrile (a, above) (1.20 g, 5.26 mmol) in 30 mL of 88% formic acid was heated to 100°C overnight. Upon cooling to room temperature, the precipitated crude product was filtered, washed with diethyl ether and dried under vacuum to yield 0.88 g (65%) of product as a white solid.

20

<sup>1</sup>H NMR (DMSO) δ 12.50 (br s, 1H), 8.40 (s, 1H), 8.25 (d, 1H), 7.65 (m, 2H), 7.45 (t, 1H), 7.00 (d, 1H), 4.10 (q, 2H), 1.40 (t, 3H) ppm; ES-MS m/z 257 (MH<sup>+</sup>).

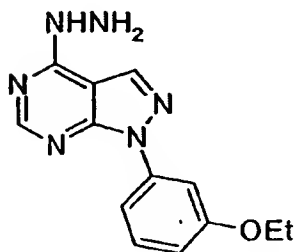
c. 4-Chloro-1-(3-ethoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine.

5

A suspension of 1-(3-ethoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-ol (b, above) (0.88 g, 3.43 mmol) in 5 mL of phosphorus oxychloride was heated at 100°C for 30 minutes. The reaction mixture was cooled to room temperature, poured into ice, and extracted with dichloromethane. The organic phase was dried over anhydrous sodium sulfate and the solvent evaporated under vacuum to give 0.94 g of product as an off-white solid.

<sup>1</sup>H NMR (DMSO) δ 9.05 (s, 1H), 8.80 (s, 1H), 7.79 (m, 2H), 7.50 (t, 1H), 7.05 (d, 1H), 4.15 (q, 2H), 1.40 (t, 3H) ppm.

15

d. 1-(3-Ethoxyphenyl)-4-hydrazino-1*H*-pyrazolo[3,4-*d*]pyrimidine.

20



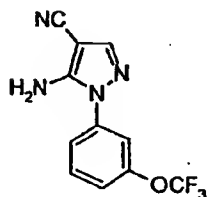
Hydrazine hydrate (1.0 mL, 20.5 mmol) was added to a suspension of 4-chloro-1-(3-ethoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (c, above) (0.94 g, 3.42 mmol) in 25 mL of absolute ethanol. The mixture was heated at reflux for 1.5 hours. After removal of solvent under vacuum, the crude solid product was suspended in saturated aqueous sodium bicarbonate, filtered, washed with water and dried under vacuum to give 0.81 g (88%) of product as a white solid.

ES-MS *m/z* 271 (*MH*<sup>+</sup>).

#### Intermediates Example M

##### 4-Hydrazino-1-[3-(trifluoromethoxy)phenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidine

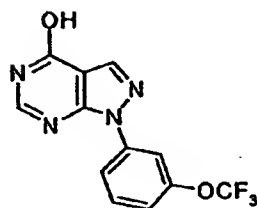
##### a. 5-Amino-1-[3-(trifluoromethoxy)phenyl]-1*H*-pyrazole-4-carbonitrile



Ethoxymethylenemalononitrile (1.72 g, 14.1 mmol) was added to a solution of 3-trifluoromethoxyphenylhydrazine (2.71 g, 14.1 mmol) in 75 mL of absolute ethanol. The mixture was heated at reflux for 1 hour, cooled and the solvent removed under vacuum. The solid residue was recrystallized from hexane/ethyl acetate to give 2.43 g (64%) of pure product.

<sup>1</sup>H NMR (DMSO) δ7.86 (s, 1H), 7.68 (t, 1H), 7.60 (d, 1H), 7.54 (s, 1H), 7.46 (d, 1H), 6.90 (br s, 2H) ppm.

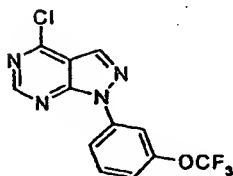
b. 1-[3-(Trifluoromethoxy)phenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-ol



5-Amino-1-[3-(trifluoromethoxy)phenyl]-1*H*-pyrazole-4-carbonitrile (a, above) (2.42 g, 9.03 mmol) was treated with formic acid as described for 1-(2-Methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-ol (Intermediates Example C) to give 1.50 g (56%) of product.

<sup>1</sup>H NMR (DMSO) δ12.60 (br s, 1H), 8.40 (s, 1H), 8.30 (s, 1H), 8.20 (m, 2H), 7.75 (t, 1H), 7.45 (d, 1H) ppm; ES-MS *m/z* 297 (MH<sup>+</sup>).

c. 4-Chloro-1-[3-(trifluoromethoxy)phenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidine



1-[3-(Trifluoromethoxy)phenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-ol (b, above) (1.49 g, 5.03 mmol) was treated with phosphorus oxychloride as described 4-Chloro-1-(2-

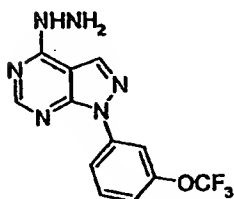
50

methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (Intermediates Example C) to give 1.45 g (92%) of product as a white solid.

<sup>1</sup>H NMR (DMSO) δ9.05 (s, 1H), 8.85 (s, 1H), 8.30 (d, 1H), 8.25 (s, 1H), 7.80 (t, 1H), 7.45 (d, 1H) ppm.

d. 4-Hydrazino-1-[3-(trifluoromethoxy)phenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidine.

10



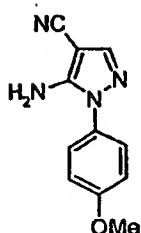
4-Chloro-1-[3-(trifluoromethoxy)phenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidine (c, above) (1.45 g, 4.61 mmol) was treated with hydrazine hydrate (1.3 mL, 27.6 mmol) as described for 4-hydrazino-1-(2-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (Intermediates Example C) to give 0.996 g (70%) of product as a white solid.

ES-MS *m/z* 311 (MH<sup>+</sup>).

20

Intermediates Example N4-Hydrazino-1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine

- 5 a. 5-Amino-1-(4-methoxyphenyl)-1H-pyrazole-4-carbonitrile.

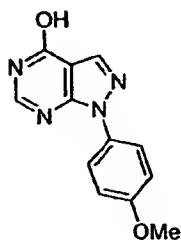


- A mixture of 4-methoxyphenylhydrazine hydrochloride (5.00 g, 28.6 mmol),  
10 ethoxymethylenemalononitrile (3.49 g, 28.6 mmol) and triethylamine (4.8 mL, 34.3 mmol) in 75 mL of absolute ethanol was heated at reflux overnight. The solvent was removed under vacuum and the residue was extracted between ethyl acetate and saturated aqueous sodium bicarbonate. The organic phase was dried over sodium sulfate and the solvent evaporated. The residue was purified by flash chromatography  
15 with hexane/ethyl acetate to give 4.88 g (80%) of product as an off-white crystalline solid.

<sup>1</sup>H NMR (DMSO) δ 7.70 (s, 1H), 7.35 (d, 2H), 7.05 (d, 2H), 6.50 (br s, 2H), 3.80 (s, 3H) ppm.

20

- b. 1-(4-Methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ol.

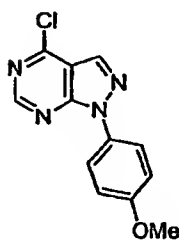


A solution of 5-amino-1-(4-methoxyphenyl)-1*H*-pyrazole-4-carbonitrile (a, above) (4.88 g, 22.8 mmol) in 100 mL of 88% formic acid was heated at 100°C overnight.

- 5 Upon cooling to room temperature, a solid precipitated. The solid was collected by filtration, washed with diethyl ether and dried under vacuum to give 3.30 g (60%) of product as a white powder.

<sup>1</sup>H NMR (DMSO) δ 12.20 (br s, 1H), 8.25 (s, 1H), 8.10 (m, 1H), 7.85 (d, 2H), 7.05 (d, 2H),  
10 3.80 (s, 3H) ppm.

c 4-Chloro-1-(4-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine



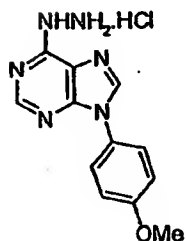
15

A suspension of 1-(4-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-ol (b, above) (3.30 g, 13.6 mmol) in 10 mL of phosphorus oxychloride was heated to 100°C for two hours. The mixture was cooled to room temperature, poured into ice, and extracted  
20 with dichloromethane. The organic phase was washed with saturated aqueous sodium bicarbonate, dried over sodium sulfate and the solvent removed to give 3.30 g (67%) of product as a white solid.

<sup>1</sup>H NMR (DMSO) δ 8.90 (s, 1H), 8.65 (s, 1H), 7.95 (s, 2H), 7.15 (d, 2H), 3.80 (s, 3H) ppm.

25

d. 4-Hydrazino-1-(4-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine.



5

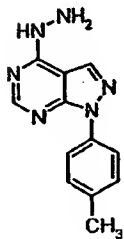
Hydrazine hydrate (3.7 mL, 76 mmol) was added to a suspension of 4-chloro-1-(4-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (c, above) (3.30 g, 12.7 mmol) in 100 mL of absolute ethanol. The mixture was heated at reflux for two hours. The solvent  
10 was evaporated to give 4.40 g of a white solid.

ES-MS *m/z* 257 (*MH*<sup>+</sup>).

15

#### Intermediates Example 0

#### 4-Hydrazino-1-(4-methylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine



20

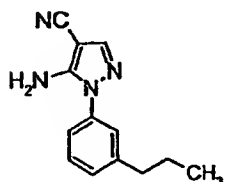
4-Chloro-1-(4-methylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (2.00 g, 8.18 mmol) was dissolved in ethanol (150 mL) and hydrazine mono-hydrate (2.47 mL, 49.1 mmol) was added. The mixture was heated at 45 C for ca. 20 h and concentrated under reduced pressure. The resulting solid was triturated with aqueous sodium bicarbonate to give the product as a white solid (1.83 g, 93 %).

ES-MS  $m/z$  241 ( $MH^+$ ).

10 Intermediates Example P

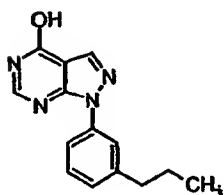
4-hydrazino-1-(3-propylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine

a. 5-Amino-1-(3-propylphenyl)-1*H*-pyrazole-4-carbonitrile



To 1-(3-Propylphenyl)hydrazine hydrochloride (1.00 g, 5.36 mmol) in 15 mL of ethanol was added 2-(ethoxymethylene)malononitrile (0.654 g, 5.36 mmol) and triethylamine (0.97 mL, 6.97 mmol). Mixture was refluxed for ca. 3.5 h, concentrated under reduced pressure and the residue was partitioned between saturated aqueous sodium bicarbonate and ethyl acetate. The product was isolated by flash chromatography as a white solid (0.79 g, 65%).

<sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  7.64 (s, 1H), 7.43 (t, 1H), 7.29 (m, 3H), 4.58 (s, 2H), 2.66 (t, 2H), 1.66 (m, 2H), 0.96 (t, 3H) ppm.

b. 1-(3-propylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-ol

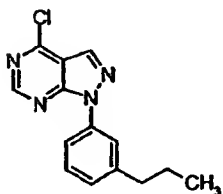
5 5-Amino-1-(3-propylphenyl)-1*H*-pyrazole-4-carbonitrile (a, above) (0.78 g, 3.45 mmol) was dissolved in 45 mL of formic acid and reflux for ca. 24 h. The mixture was cooled to RT, concentrated under reduced pressure and diluted with ether. The resulting solid were collected by filtration and washed with ether to give the product as a white solid (0.53 g, 60%).

10

<sup>1</sup>H NMR (DMSO) δ 12.44 (s, 1H), 8.31 (s, 1H), 8.20 (d, 1H), 7.85 (m, 2H), 7.44 (t, 1H), 7.22 (d, 1H), 2.64 (t, 2H), 1.64 (m, 2H), 0.91 (t, 3H) ppm.

c. 4-chloro-1-(3-propylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine

15

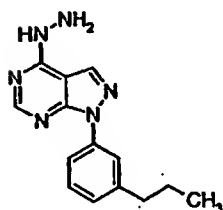


1-(3-Propylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-ol (b, above) (0.52 g, 2.03 mmol)  
20 was dissolved in phosphorous oxychloride (10 mL) and 2-3 drops of DMF was added. The mixture was heated at reflux for ca. 3.5 h. The mixture was concentrated under reduced pressure, quenched into an ice/sodium bicarbonate mixture and extracted with methylene chloride. The organic phase was washed with aqueous sodium bicarbonate and concentrated to give the product as a white solid (0.53g, 96%).



<sup>1</sup>H NMR (DMSO)  $\delta$  8.99 (s, 1H), 8.75 (s, 1H), 7.96 (m, 2H), 7.51 (t, 1H), 7.27 (d, 1H), 2.67 (t, 2H), 1.64 (m, 2H), 0.92 (t, 3H) ppm. ES-MS  $m/z$  273 (MH<sup>+</sup>).

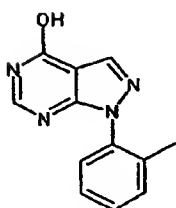
5 d. 4-hydrazino-1-(3-propylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine



- 10 4-Chloro-1-(3-propylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (c, above) (0.55 g, 2.02 mmol) was dissolved in ethanol (50 mL) and hydrazine mono-hydrate (0.60 mL, 12.3 mmol) was added. The mixture was heated at 45 C for ca. 19 h and concentrated under reduced pressure. The resulting solid was triturated with aqueous sodium bicarbonate to give the product as a white solid (0.48 g, 90 %). ES-MS  $m/z$  269 (MH<sup>+</sup>).

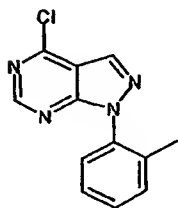
Intermediates Example Q4-Hydrazino-1-(2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidine hydrochloride

- 5 a. 1-(2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ol



- 10 Prepared from 5-amino-1-(2-methylphenyl)-1H-pyrazole-4-carbonitrile using the method described for 1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ol (Intermediates Example N).

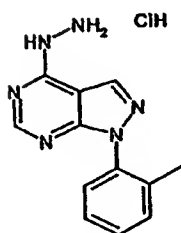
- 15 b. 4-Chloro-1-(2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidine



- 20 Prepared from 1-(2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ol (a, above) using the method described for 4-Chloro-1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine (Intermediates Example N).

<sup>1</sup>H NMR (300 MHz, DMSO) δ 8.84 (s, 1H), 8.72 (s, 1H), 7.39-7.48 (m, 4H), 2.04 (s, 3H) ppm. ES-MS m/z 245 (MH<sup>+</sup>).

c. 4-Hydrazino-1-(2-methylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine  
hydrochloride



10 Prepared from 4-Chloro-1-(2-methylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (b, above)  
using the method described for 4-hydrazino-1-(4-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (Intermediates Example N).

<sup>1</sup>H NMR (300 MHz, DMSO) δ 9.28 (s, 1H), 8.56 (s, 1H), 8.34 (s, 1H), 8.09 (s, 1H), 7.38-7.45 (m, 4H), 5.04 (s, 2H), 2.08 (s, 3H) ppm. ES-MS *m/z* 241 (MH<sup>+</sup>).

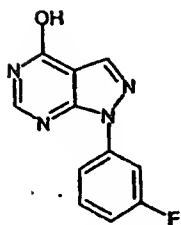
15 Intermediates Example R

1-(3-fluorophenyl)-4-hydrazino-1*H*-pyrazolo[3,4-*d*]pyrimidine

20

a. 1-(3-fluorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-ol

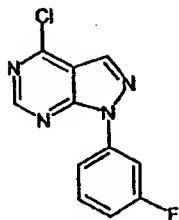
59



Prepared from 5-amino-1-(3-fluorophenyl)-1*H*-pyrazole-4-carbonitrile using the method described for 1-(4-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-ol (Intermediates Example N).

5

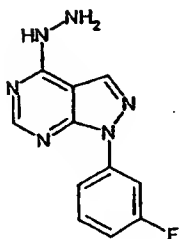
b. 4-chloro-1-(3-fluorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine



10 Prepared from 1-(3-fluorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-ol (a, above) using the method described for 4-chloro-1-(4-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (Intermediates Example N).

c. 1-(3-fluorophenyl)-4-hydrazino-1*H*-pyrazolo[3,4-*d*]pyrimidine

15



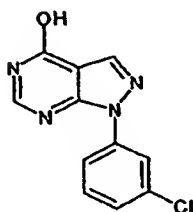
60

Prepared from 4-chloro-1-(3-fluorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (b, above) using the method described for 1-(4-methoxyphenyl)-4-hydrazino-1*H*-pyrazolo[3,4-*d*]pyrimidine (Intermediates Example N).

5

Intermediates Example S1-(3-chlorophenyl)-4-hydrazino-1*H*-pyrazolo[3,4-*d*]pyrimidine

10

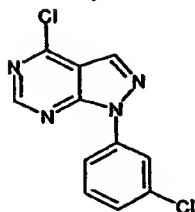
a. 1-(3-Chlorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-ol

15

Prepared from 5-amino-1-(3-chlorophenyl)-1*H*-pyrazole-4-carbonitrile using the method described for 1-(4-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-ol (Intermediates Example N).

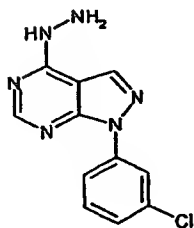
20 <sup>1</sup>H NMR (400 MHz, DMSO) δ 12.50 (s, 1H), 8.32 (s, 1H), 8.21 (s, 1H), 8.16 (m, 1H), 8.01 (d, 1H), 7.55 (t, 1H), 7.41 (d, 1H) ppm. ES-MS *m/z* 247 (MH<sup>+</sup>).

b. 4-chloro-1-(3-chlorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine



- 5 Prepared from 1-(3-Chlorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-ol (a, above) using the method described for 4-chloro-1-(4-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (Intermediates Example N).

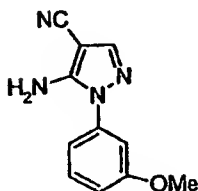
10 c. 1-(3-chlorophenyl)-4-hydrazino-1*H*-pyrazolo[3,4-*d*]pyrimidine



- 15 Prepared from 4-chloro-1-(3-chlorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (b, above) using the method described for 1-(4-methoxyphenyl)-4-hydrazino-1*H*-pyrazolo[3,4-*d*]pyrimidine (Intermediates Example N).

Intermediates Example T4-Hydrazino-1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine

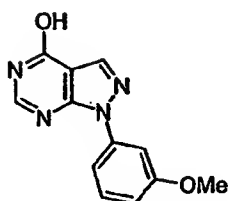
- 5 a. 5-amino-1-(3-methoxyphenyl)-1H-pyrazole-4-carbonitrile



- 10 A mixture of 3-methoxyphenylhydrazine hydrochloride (5.00 g, 28.6 mmol), ethoxymethylenemalononitrile (3.49 g, 28.6 mmol), and triethylamine (4.8 mL, 34.3 mmol) in 75 mL of absolute ethanol was heated at reflux for 18 hours. The reaction mixture was cooled to room temperature and the solvent was removed under vacuum. The residue was extracted between ethyl acetate and saturated aqueous sodium
- 15 bicarbonate. The organic phase was concentrated under vacuum to give a brown paste. Flash chromatography on silica gel with hexane:ethyl acetate (70:30) gave 4.54 g (74%) of product as a light tan solid.

<sup>1</sup>H NMR (400 MHz, DMSO) 8.780 (s, 1H), 7.40 (t, 1H), 7.05 (d, 1H), 7.00 (s, 1H), 6.95 (d, 1H), 6.65 (br s, 2H), 3.80 (s, 3H) ppm.

20

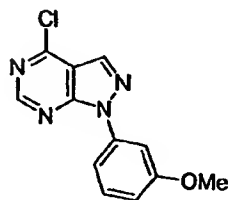
b. 1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-ol

5

A solution of 5-amino-1-(3-methoxyphenyl)-1*H*-pyrazole-4-carbonitrile (a, above) (4.50 g, 21.0 mmol) in 100 mL of 88% formic acid was heated at 100°C under nitrogen for 18 hours. The reaction mixture was cooled to room temperature and diluted with  
10 100 mL of diethyl ether. The resulting precipitate was filtered, washed with ether and dried under vacuum to give 3.67 g (72%) of product as an off-white solid.

<sup>1</sup>H NMR (400 MHz, DMSO) δ 12.50 (br s, 1H), 8.40 (s, 1H), 8.25 (m, 1H), 7.70 (m, 2H), 7.50 (t, 1H), 7.0 (dd, 1H), 3.9 (s, 3H) ppm.

15

c. 4-chloro-1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine

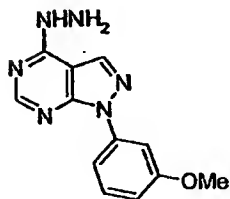
A suspension of 1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-ol (b, above) (3.38 g, 13.9 mmol) in 15 mL of phosphorus oxychloride was heated at 100°C for 30 minutes. After cooling to room temperature the reaction mixture was poured into ice and extracted with dichloromethane. The organic phase was dried over anhydrous  
20



sodium sulfate, filtered, and the solvent removed under vacuum to give 3.49 g (96%) of product as a light tan solid.

<sup>1</sup>H NMR (400 MHz, DMSO)  $\delta$  9.0 (s, 1H), 8.75 (s, 1H), 7.75 (m, 2H), 7.50 (t, 1H), 7.0 (d, 1H), 3.85 (s, 3H) ppm.

d. 4-Hydrazino-1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine



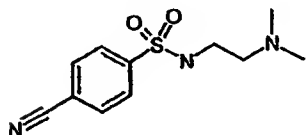
10

Hydrazine hydrate (3.9 mL, 80.4 mmol) was added to a suspension of 4-chloro-1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (c, above) in 100 mL of absolute ethanol. The mixture was heated at reflux for 2.5 hours. The resulting solution was cooled to room temperature and the solvent was removed under vacuum. The residue was suspended in saturated aqueous sodium bicarbonate and stirred for 10 minutes. The mixture was filtered and the solid was washed with water, and dried under vacuum for 18 hours to give 2.91g (85%) of product as a white solid.

15

ES-MS *m/z* 257 (MH<sup>+</sup>).

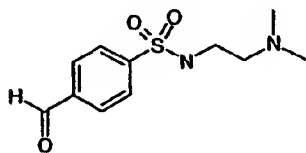
20

Intermediates Example U*N*-[2-(dimethylamino)ethyl]-4-formylbenzenesulfonamidea. 4-cyano-*N*-[2-(dimethylamino)ethyl]benzenesulfonamide

(U16945/187/1)

10 *N,N*-dimethylethylenediamine (3.40 mL; 31.10 mmol) was added to a solution of 4-cyanobenzenesulfonyl chloride (2.50 g; 12.40 mmol) in THF (25 mL) at RT. After 16h, saturated NaHCO<sub>3</sub> (100 mL) and ethylacetate (250 mL) were added. The organic layer was separated, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give the title compound (3.00 g; 96%).

15 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.98 (s, 2H), 7.80 (d, 2H), 5.25 (s br, 1H), 2.98 (t, 2H), 2.33 (t, 2H), 2.07 (s, 6H).

b. *N*-[2-(dimethylamino)ethyl]-4-formylbenzenesulfonamide

(U16945/187/2)

20 A solution of 1M diisobutylaluminum hydride in hexanes (9.57 mL; 9.57 mmol) was added slowly to a solution of 4-cyano-*N*-[2-(dimethylamino)ethyl]benzenesulfonamide (a, above) (1.10 g; 4.35 mmol) in toluene (50 mL) at RT under N<sub>2</sub>. After 3h, an aqueous solution of 5% H<sub>2</sub>SO<sub>4</sub> (50 mL) was added

and the mixture was stirred for 1h. Saturated  $\text{NaHCO}_3$  (100 mL) and ethylacetate (200 mL) were added. The aqueous layer was separated and extracted with ethylacetate. The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated to give the title compound (0.89 g; 80%).

5

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  10.09 (s, 1H), 8.04–7.99 (m, 4H), 4.96 (s br, 1H), 2.99 (t, 2H), 2.32 (t, 2H), 2.06 (s, 6H).

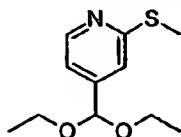
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#### Intermediates Example V

##### 4-(diethoxymethyl)-2-(methylsulfonyl)pyridine

##### a. 4-(diethoxymethyl)-2-(methylthio)pyridine

15



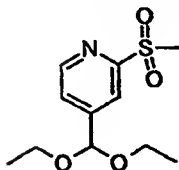
20

To 2-chloro-4-(diethoxymethyl)pyridine (0.214 g, 1.0 mmol) in THF was added sodium thiomethoxide ((0.35 g, 5 mmol) and the mixture was refluxed for ca. 16 h. The mixture was quenched into aqueous sodium bicarbonate and extracted with ethyl acetate. The product was purified by silica gel chromatography (20:1 hexanes:ethyl acetate) to give the product as a clear oil (0.12 g, 54%).

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  8.43 (d, 1H), 7.27 (s, 1H), 7.08 (d, 1H), 5.43 (s, 1H), 3.56 (m, 4H), 2.57 (s, 3H), 1.24 (t, 6H) ppm.

25

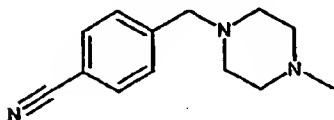
## b. 4-(diethoxymethyl)-2-(methylsulfonyl)pyridine



- 4-(diethoxymethyl)-2-(methylthio)pyridine (a, above) (0.12 g, 0.522 mmol) in methylene chloride (10 mL) was cooled in a 0 °C bath and MCPBA (0.24 g of 75%, 1.04 mmol) was added in 4 portions over 10 min. The mixture was stirred at 0 °C for ca. 2.5 h and then partitioned between aqueous sodium bicarbonate and methylene chloride. The product was purified by silica gel chromatography (1:1 ethyl acetate: hexanes) to give the product as a clear oil (0.12 g, 89%).
- <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.73 (d, 1H), 8.20 (s, 1H), 7.67 (d, 1H), 5.56 (s, 1H), 3.59 (m, 4H), 3.25 (s, 3H), 1.27 (t, 6H) ppm.

15 Intermediates Example W4-[(4-methylpiperazin-1-yl)methyl]benzaldehyde

## a. 4-[(4-methylpiperazin-1-yl)methyl]benzonitrile



20

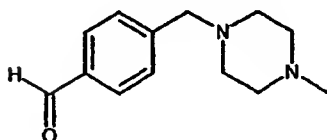
- 4-[(diethylamino)methyl]benzonitrile (250 mg, 1.28 mmol) in DMF (25 mL) was treated with 1-methylpiperazine (191 mg, 1.91 mmol) followed by potassium carbonate (177 mg, 1.28 mmol). The mixture was stirred at RT for ca. 18 h. The reaction was concentrated and then partitioned between water and ethyl acetate. The aqueous

25

layer was extracted with ethyl acetate. The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$ , and concentrated to give pure product as a white solid (189mg, yield 69%).

$^1\text{H}$  NMR (300 MHz, DMSO)  $\delta$  7.78 (d, 2H), 7.49 (d, 2H), 3.53 (s, 2H), 2.44–2.21 (m, 8H),  
5 2.14 (s, 3H).

b. 4-[[4-methylpiperazin-1-yl)methyl]benzaldehyde



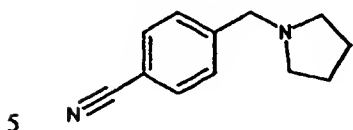
10

4-[[4-methylpiperazin-1-yl)methyl]benzonitrile (189 mg, 0.88 mmol) in toluene (15 mL) was treated with DIBAL (1M in heptane, 1.93 mL) and stirred at RT for 1 h. An aqueous solution of 5%  $\text{H}_2\text{SO}_4$  (30 mL) was added and the reaction was stirred for ca.  
15 18h. The pH was adjusted with aqueous sodium bicarbonate and extracted with ethyl acetate then chloroform:isopropanol (4:1). The organic layers were combined, dried, and concentrated to give pure product as a thick oil (187 mg, yield 97%).

$^1\text{H}$  NMR (300 MHz, DMSO)  $\delta$  9.98 (s, 1H), 7.86 (d, 2H), 7.52 (d, 2H), 3.54 (s, 2H), 2.44–  
20 2.21 (m, 8H), 2.14 (s, 3H).

Intermediates Example X4-(pyrrolidin-1-ylmethyl)benzaldehyde

## a. 4-(pyrrolidin-1-ylmethyl)benzonitrile

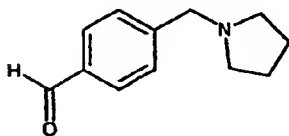


4-[(diethylamino)methyl]benzonitrile (250mg, 1.28 mmol) was treated with pyrrolidine (136 mg, 1.19 mmol) as described for 4-[[4-methylpiperazin-1-yl)methyl]benzonitrile (Intermediates Example W) to give pure product as a yellow oil (112 mg, yield 47%).

10

<sup>1</sup>H NMR (300 MHz, DMSO) δ 7.77 (d, 2H), 7.50 (d, 2H), 3.65 (s, 2H), 2.50–2.35 (m, 4H), 1.75–1.65 (m, 4H).

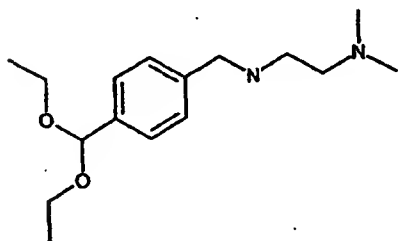
## b. 4-(pyrrolidin-1-ylmethyl)benzaldehyde



4-(pyrrolidin-1-ylmethyl)benzonitrile (112 mg, 0.60 mmol) was treated with DIBAL as described for 4-[[4-methylpiperazin-1-yl)methyl]benzaldehyde (Intermediates Example W) to give pure product as a thick oil (111 mg, yield 98%).

20

<sup>1</sup>H NMR (300 MHz, DMSO) δ 9.98 (s, 1H), 7.76 (d, 2H), 7.53 (d, 2H), 3.66 (s, 2H), 2.47–2.38 (m, 4H), 1.75–1.65 (m, 4H).

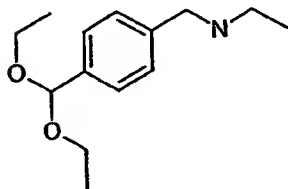
Intermediates Example Y*N*-[4-(diethoxymethyl)benzyl]-*N,N*-dimethylethane-1,2-diamine

5

A solution of 4-(diethoxymethyl)benzaldehyde (500 mg, 2.4 mmol), methanol (10 mL), THF (10 mL), and *N,N*-dimethylethane-1,2-diamine (0.39 mL, 3.6 mmol) was stirred at RT for 3h. Sodium borohydride (230 mg, 6.0 mmol) was added and the reaction was refluxed for 3h. The resulting mixture was made basic with sat. sodium bicarb, and  
10 extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate and concentrated to give pure product (595 mg, yield 89%).

<sup>1</sup>H NMR (300 MHz, DMSO)  $\delta$  7.31 (s, 2H), 7.30 (s, 2H), 5.45 (s, 1H), 3.68 (s, 2H), 3.58-3.42 (m, 4H), 2.56-2.46 (m, 2H), 2.24-2.36 (m, 2H), 2.09 (s, 6H), 2.13 (s, 6H).

15

Intermediates Example Z*N*-[4-(diethoxymethyl)benzyl]ethanamine

20 U17724/152/1

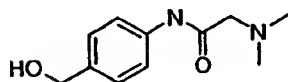
A solution of 4-(diethoxymethyl)benzaldehyde (0.48 mL, 2.4 mmol), methanol (10 mL), THF (10 mL), and 2N ethylamine/THF (3.15 mL, 3.6 mmol) was stirred at RT for 2h.

Sodium borohydride (230 mg, 6.0 mmol) was added and the reaction was stirred at RT overnight. The resulting mixture was made basic with sat. sodium bicarb, and extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate and concentrated to give pure product as an oil (345 mg, yield 61%).

5

Intermediates Example AA*N*'-(4-formylphenyl)-*N*<sup>2</sup>,*N*<sup>2</sup>-dimethylglycinamidea. *N*'-[4-(hydroxymethyl)phenyl]-*N*<sup>2</sup>,*N*<sup>2</sup>-dimethylglycinamide

10

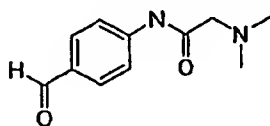


A mixture of (4-aminophenyl)methanol (200 mg, 1.10 mmol), *N,N*-dimethylglycyl chloride (200 mg, 1.65 mmol) and triethylamine (0.43 mL, 3.3 mmol) in dichloromethane (5 mL) was stirred at RT for 1 h. The reaction mixture was concentrated and purified by silica gel flash chromatography (gradient elution: 100% → 99% → 95% dichloromethane in methanol) to provide the title compound as a yellow solid (182 mg, 79% yield).

15

<sup>1</sup>H NMR (400 MHz, DMSO): δ 9.67 (s, 1H), 7.56 (d, 2H), 7.21 (d, 2H), 5.07 (t, 1H), 4.40 (d, 2H), 3.08 (s, 2H), 2.28 (s, 6H).

20

b. *N*'-(4-formylphenyl)-*N*<sup>2</sup>,*N*<sup>2</sup>-dimethylglycinamide

25

A mixture of *N*'-[4-(hydroxymethyl)phenyl]-*N*<sup>2</sup>,*N*<sup>2</sup>-dimethylglycinamide (a, above) (182 mg, 0.873 mmol) and manganese (IV) dioxide (1.52 g, 17.48 mmol) in dichloromethane



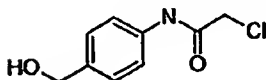
(10 mL) was stirred at RT for 18 h. The reaction mixture was filtered through a pad of Celite 545®, and the filtrate was concentrated to give product as a brown oil (106 mg, 60% yield).

- 5 <sup>1</sup>H NMR (400 MHz, DMSO): δ 10.14 (s, 1H), 9.86 (s, 1H), 7.85 (m, 4H), 3.11 (s, 2H), 2.26 (s, 6H).

#### Intermediates Example BB

10 *N*-(4-formylphenyl)-2-morpholin-4-ylacetamide

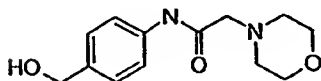
- a. 2-chloro-*N*-[4-(hydroxymethyl)phenyl]acetamide



- 15 A mixture of (4-aminophenyl)methanol (500 mg, 4.06 mmol) and chloroacetyl chloride (1.41 mL, 17.86 mmol) in acetonitrile (150 mL) was stirred at RT for 15 min. The reaction was then partitioned between ethyl acetate and sat. aq. NaHCO<sub>3</sub>. The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated, and the residue purified by silica gel flash chromatography (40% ethyl acetate in hexanes) to provide product as a yellow solid
- 20 (1.3 g, 40% yield).

<sup>1</sup>H NMR (400 MHz, DMSO): δ 10.24 (s, 1H), 7.51 (d, 2H), 7.24 (d, 2H), 5.11 (s, 1H), 4.41 (s, 2H) 4.22 (s, 2H).

- 25 b. *N*-[4-(hydroxymethyl)phenyl]-2-morpholin-4-ylacetamide

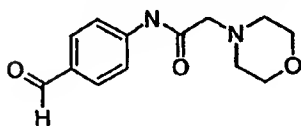


A mixture of 2-chloro-*N*-[4-(hydroxymethyl)phenyl]acetamide (a, above) (128 mg, 0.641 mmol) and morpholine (0.2 mL, 1.923 mmol) in ethanol (10 mL) was heated to 100 °C for 2 h. The reaction was then cooled to RT and concentrated to provide product (160 mg, 100% yield) as a yellow oil (160 mg, 100% yield).

5

<sup>1</sup>H NMR (400 MHz, DMSO): δ 9.68 (s, 1H), 7.55 (d, 2 H), 7.21 (d, 2H), 5.09 (s, 1H), 4.41 (s, 2H), 3.62 (m, 4H), 3.09 (s, 2H), 2.88 (t, 4H).

c. *N*-(4-formylphenyl)-2-morpholin-4-ylacetamide



10

A solution of *N*-[4-(hydroxymethyl)phenyl]-2-morpholin-4-ylacetamide (b, above) (334 mg, 1.33 mmol) in dichloromethane (7 mL) was added via cannula transfer to a solution of dimethyl sulfoxide (206 µL, 2.66 mmol) and oxalyl chloride (2M in dichloromethane, 670 µL) in dichloromethane (6 mL) at -78 °C. The reaction mixture was stirred at this temperature for 15 min and then at -40 °C for 40 min.

15

Triethylamine (610 µL, 4.39 mmol) was added and the reaction was stirred at this temperature for 5 min and then warmed to RT. The mixture was diluted with water and extracted with dichloromethane. The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated, and the residue purified by silica gel flash chromatography (4% methanol in dichloromethane) to provide product as a yellow oil (112 mg, 34% yield).

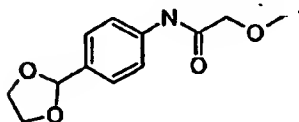
20

<sup>1</sup>H NMR (400 MHz, DMSO): δ 10.14 (s, 1H), 9.85 (s, 1H), 7.84 (s, 4H), 3.61 (t, 4H), 3.33 (s, 2H), 3.14 (t, 4H). ES-MS m/z 249 (MH<sup>+</sup>).

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Intermediates Example CC*N*-(4-formylphenyl)-2-methoxyacetamidea. *N*-[4-(1,3-dioxolan-2-yl)phenyl]-2-methoxyacetamide

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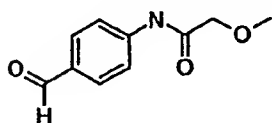


Methoxyacetyl chloride (0.6 mL, 6.36 mmol) was added to a mixture of 4-(1,3-dioxolan-2-yl)aniline (500 mg, 3.03 mmol) and pyridine (0.6 mL, 6.36 mmol) in diethyl ether (10 mL) at 0 °C. The reaction was stirred at this temperature for 20 min and then partitioned between ethyl acetate and satd. aq. NaHCO<sub>3</sub>. The organic layer was dried (MgSO<sub>4</sub>) and concentrated, and the residue purified by silica gel flash chromatography (30% ethyl acetate in hexanes) to provide product as a yellow solid (434 mg, 64% yield).

<sup>1</sup>H NMR (400 MHz, DMSO): δ 9.81 (s, 1H), 7.65 (d, 2H), 7.33 (d, 2H), 5.63 (s, 1H), 4.00 (m, 2H), 3.97 (s, 3H), 3.90 (m, 2H).

b. *N*-(4-formylphenyl)-2-methoxyacetamide

20



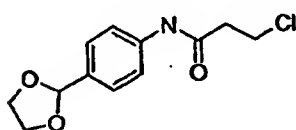
A mixture of *N*-[4-(1,3-dioxolan-2-yl)phenyl]-2-methoxyacetamide (a, above) (200 mg, 0.895 mmol) and carbon tetrabromide (59 mg, 0.179 mmol) in water (1.79 mL) and acetonitrile (0.89 mL) was heated to 90 °C for 3 h. The reaction was then diluted with water and extracted with diethyl ether. The organic layer was dried (MgSO<sub>4</sub>) and concentrated to provide product as an orange oil (160 mg, 100% yield).

<sup>1</sup>H NMR (400 MHz, DMSO): δ 10.18 (s, 1H), 9.85 (s, 1H), 7.85 (dd, 4H), 4.03 (s, 3H).

### Intermediates Example DD

#### 5 *N*'-(4-formylphenyl)-*N*<sup>β</sup>,*N*<sup>β</sup>-dimethyl-β-alaninamide

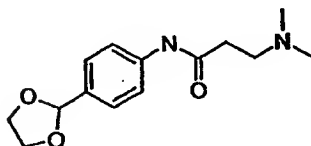
##### a. 3-chloro-*N*'-[4-(1,3-dioxolan-2-yl)phenyl]propanamide



10 A solution of chloropropionyl chloride (0.64 mL, 6.65 mmol) in dichloromethane (1 mL) was added to a mixture of 4-(1,3-dioxolan-2-yl)aniline (1.0 g, 6.05 mmol) and pyridine (1.5 mL, 18.15 mmol) in diethyl ether (25 mL) at 0 °C. The reaction was stirred at this temperature for 10 min and then partitioned between ethyl acetate and satd. aq. NaHCO<sub>3</sub>. The organic layer was dried (MgSO<sub>4</sub>) and concentrated, and the residue purified by silica gel flash chromatography (30% ethyl acetate in hexanes) to provide  
15 product as a yellow solid (730 mg, 47% yield).

<sup>1</sup>H NMR (400 MHz, DMSO): δ 10.12 (s, 1H), 7.58 (d, 2H), 7.34 (d, 2H), 5.63 (s, 1H), 4.00 (m, 2H), 3.88 (m, 4H), 2.80 (t, 2H). ES-MS m/z 256 (MH<sup>+</sup>).

##### 20 b. *N*'-[4-(1,3-dioxolan-2-yl)phenyl]-*N*<sup>β</sup>,*N*<sup>β</sup>-dimethyl-β-alaninamide



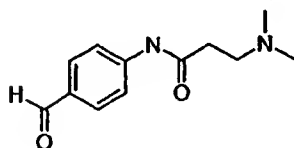
25 A mixture of 3-chloro-*N*'-[4-(1,3-dioxolan-2-yl)phenyl]propanamide (a, above) (200 mg, 0.782 mmol), *N*-ethyl-*N*-isopropylpropan-2-amine (0.41 mL, 2.364 mmol) and 2M dimethylamine (0.78 mL, 1.564) in dimethylformamide (10 mL) was stirred at 60 °C for

76

1 h. Additional 2M dimethylamine (0.78 mL, 1.564, 2 equiv) was added and the reaction was stirred at this temperature for 3 h. The reaction was then cooled to RT and concentrated to provide product as a yellow oil (207 mg, 100% yield).

5 <sup>1</sup>H NMR (400 MHz, DMSO): δ 10.38 (s, 1H), 7.60 (d, 2H), 7.35 (d, 2H), 5.63 (s, 1H), 4.00 (m, 2H), 3.92 (m, 2H), 3.31 (t, 2H), 2.85 (t, 2H), 2.74 (s, 6H).

c. *N*'-[4-formylphenyl]-*N*<sup>o</sup>,*N*<sup>o</sup>-dimethyl- $\beta$ -alaninamide



10

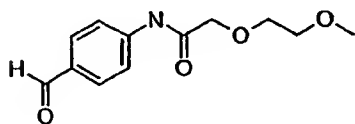
A mixture of *N*'-[4-(1,3-dioxolan-2-yl)phenyl]-*N*<sup>o</sup>,*N*<sup>o</sup>-dimethyl- $\beta$ -alaninamide (b, above) (207 mg, 0.782 mmol) and carbon tetrabromide (52 mg, 0.156 mmol) in water (1.56 mL) and acetonitrile (0.78 mL) was heated to 90 °C for 4 h. The reaction was then diluted with water and concentrated to provide product as an orange oil (172  
15 mg, 100% yield).

<sup>1</sup>H NMR (400 MHz, DMSO): δ 10.78 (s, 1H), 9.86 (s, 1H), 7.84 (quartet, 4 H), 3.36 (s, 6H), 2.92 (t, 2H), 2.75 (d, 1H), 2.46 (d, 1H). ES-MS *m/z* 221 (MH<sup>+</sup>).

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#### Intermediates Example EE

#### *N*'-[4-formylphenyl]-2-(2-methoxyethoxy)acetamide



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A solution of (2-methoxyethoxy)acetyl chloride (231 mg, 1.513 mmol) in dichloromethane (2 mL) was added dropwise to a mixture of 4-(1,3-dioxolan-2-

- yl)aniline (250 mg, 1.513 mmol) and pyridine (245  $\mu$ L, 3.026 mmol) in dichloromethane (10 mL) at 0 °C. The reaction mixture was stirred at this temperature for 1 h and then at RT for 1.5 h. The mixture was then concentrated and the residue purified by silica gel flash chromatography (25% ethyl acetate in hexanes) to provide product as a yellow oil (70 mg, 26% yield).

<sup>1</sup>H NMR (400 MHz, DMSO):  $\delta$  10.06 (s, 1H), 9.86 (s, 1H), 7.84 (m, 4H), 4.11 (s, 2H), 3.65 (dd, 2H), 3.50 (dd, 2H), 3.26 (s, 3H).

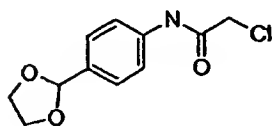
10

Intermediates Example FF

*N*-(4-formylphenyl)-2-(4-methylpiperazin-1-yl)acetamide

- a. 2-chloro-*N*-(4-(1,3-dioxolan-2-yl)phenyl)acetamide

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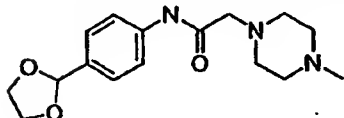


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A mixture of 4-(1,3-dioxolan-2-yl)aniline (1.0 g, 6.05 mmol), chloroacetyl chloride (0.5 mL, 6.66 mmol) and pyridine (1.5 mL, 18.15 mmol) in diethyl ether (10 mL) was stirred at 0 °C for 30 min. The reaction was partitioned between ethyl acetate and satd. aq. NaHCO<sub>3</sub>. The organic layer was dried (MgSO<sub>4</sub>) and concentrated, and the residue was purified by silica gel flash chromatography (30% ethyl acetate in hexanes) to provide product as a yellow solid (810 mg, 55% yield).

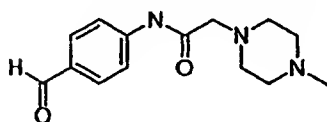
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<sup>1</sup>H NMR (400 MHz, DMSO):  $\delta$  10.36 (s, 1H), 7.58 (d, 2H), 7.37 (d, 2H), 5.65 (s, 1H), 4.23 (s, 2H), 4.01 (m, 2H), 3.90 (m, 2H).

b. *N*-[4-(1,3-dioxolan-2-yl)phenyl]-2-(4-methylpiperazin-1-yl)acetamide

A mixture of 2-chloro-*N*-[4-(1,3-dioxolan-2-yl)phenyl]acetamide (a, above) (200 mg, 0.827 mmol), 1-methylpiperazine (0.28 mL, 2.481 mmol) and pyridine (0.13 mL, 1.654 mmol) in ethanol (20 mL) was heated to reflux for 7 h. The reaction was concentrated and the residue purified by silica gel flash chromatography (20% methanol in dichloromethane) to provide product as a yellow solid (189 mg, 80% yield).

<sup>1</sup>H NMR (400 MHz, DMSO): δ 9.73 (s, 1H), 7.61 (d, 2H), 7.34 (d, 2H), 5.63 (s, 1H), 4.01 (m, 2H), 3.94 (m, 2H), 3.10 (m, 6H), 2.35 (m, 2H), 2.15 (s, 3H).

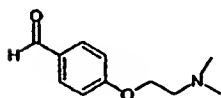
c. *N*-(4-formylphenyl)-2-(4-methylpiperazin-1-yl)acetamide

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A mixture of *N*-[4-(1,3-dioxolan-2-yl)phenyl]-2-(4-methylpiperazin-1-yl)acetamide (b, above) (189 mg, 0.619 mmol) and carbon tetrabromide (41 mg, 0.124 mmol) in water (1.24 mL) and acetonitrile (0.62 mL) was heated to 90 °C for 4 h. The reaction was then diluted with water and concentrated to provide product as an orange oil (162 mg, 100% yield).

20

<sup>1</sup>H NMR (400 MHz, DMSO): δ 10.19 (s, 1H), 9.86 (s, 1H), 7.83 (m, 4H), 4.43 (s, 2H), 3.28 (m, 4H), 2.74 (m, 2H), 2.63 (s, 3H). ES-MS *m/z* 262 (MH<sup>+</sup>).

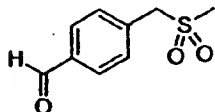
Intermediates Example GG4-[2-(dimethylamino)ethoxy]benzaldehyde

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To a mixture of 4-hydroxybenzaldehyde (1.34 g, 10.97 mmol) and 2-dimethylaminoethyl chloride hydrochloride (1.95 g, 13.54 mmol) in DMF (12 mL) was added  $K_2CO_3$  (6.04 g, 3.23 mmol). The mixture was heated at reflux for 12 h. The residue was partitioned between  $H_2O$  and EtOAc. The organic layer was dried ( $MgSO_4$ ), filtered, and concentrated. The crude material was purified by flash chromatography (10% MeOH/ $CH_2Cl_2$ ) to yield 4-[2-(dimethylamino)ethoxy]benzaldehyde (220 mg, 10%) as an orange liquid.

$^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  9.87 (s, 1H), 7.82 (d, 2H), 7.01 (d, 2H), 4.16 (t, 2H), 2.79 (t, 2H), 2.37 (s, 6H).

15

Intermediates Example HH4-[[methylsulfonyl)methyl]benzaldehyde

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U18806/48/1

A mixture of 4-(bromomethyl)benzaldehyde (100 mg, 0.503 mmol) and sodium methanesulfinate (56 mg, 0.553 mmol) in ethanol (5 mL) was heated to 100 °C for 2 h. The reaction mixture was then partitioned between ethyl acetate and water. The organic layer was washed with saturated aqueous sodium chloride, dried ( $Na_2SO_4$ ) and concentrated to provide product as a white solid (85 mg, 85% yield).

25

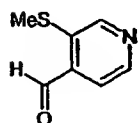


<sup>1</sup>H NMR (400 MHz, DMSO) δ 10.01 (s, 1H), 7.93 (d, 2H), 7.62 (d, 2H), 4.62 (s, 2H), 2.93 (s, 3H).

5

### Intermediates Example JJ

#### 3-methylisonicotinaldehyde



10

A solution of Dibal-H (5.62 mL, 5.62mmol) in THF was added to 3-(methylthio)isonicotinonitrile (0.510 g, 3.75 mmol) in toluene (25 mL). After 2h, a 5% H<sub>2</sub>SO<sub>4</sub> solution (50 mL) was added and stirred for 16h. A solution of 1N NaOH was added until pH was basic, then the mixture was extracted with ethyl acetate (100 mL). Organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give title compound in ~40% purity by LC/MS.

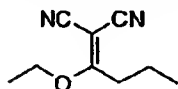
15

### Intermediates Example KK

#### 4-Hydrazino-1-(3-methoxyphenyl)-3-propyl-1H-pyrazolo[3,4-d]pyrimidine

20

##### a. 2-(1-Ethoxybutylidene)malononitrile

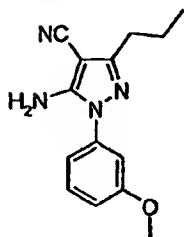


A mixture of triethylorthobutyrate (6.9 mL, 31.9 mmole) and malonitrile (2.00 mL, 31.8 mmole) was heated to 140°C for 30 minutes. During the course of the reaction ethanol was removed by distillation. Cooling the reaction mixture provided the product as a yellow oil (5.02 g, 96%).

25

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 4.42 (q, 2H), 2.60 (t, 2H), 1.67 (m, 2H), 1.44 (t, 3H), 1.04 (t, 3H) ppm.

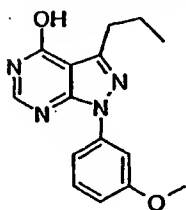
## b. 5-Amino-1-(3-methoxyphenyl)-3-propyl-1H-pyrazole-4-carbonitrile



To a solution of 2-(1-ethoxybutylidene)malononitrile (a, above) (2.836 g, 17.3 mmole) in ethanol (65 mL) was added 3-methoxyphenylhydrazine hydrochloride (3.016 g, 17.3 mmole) and triethylamine (5.00 mL, 35.9 mmole). The resulting solution was heated to reflux for 3 hours, then cooled to RT and concentrated. The residue was partitioned between saturated aqueous sodium bicarbonate and ethyl acetate (2:1, 150 mL). The aqueous layer was extracted with ethyl acetate (1 x 50 mL) and the combined organics were dried (MgSO<sub>4</sub>) and concentrated. The crude product was purified by silica gel chromatography to provide the product as a red oil (3.49 g, 79%).

<sup>1</sup>H NMR (DMSO): δ 7.38 (t, 1H), 7.04 (dd, 1H), 7.00 (m, 1H), 6.94 (dd, 1H), 6.63 (s, 2H), 3.79 (s, 3H), 2.48 (t, 2H), 1.64 (m, 2H), 0.92 (t, 3H) ppm.

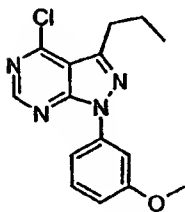
## c. 1-(3-Methoxyphenyl)-3-propyl-1H-pyrazolo[3,4-d]pyrimidin-4-ol



A solution of 5-amino-1-(3-methoxyphenyl)-3-propyl-1H-pyrazole-4-carbonitrile (b, above) (3.49 g, 13.6 mmole) in formic acid (50 mL) was heated to reflux overnight. Upon cooling to RT the solution was concentrated. The residue was triturated with ether to provide the product as a pale pink solid (2.32 g, 60%).

<sup>1</sup>H NMR (DMSO): δ 12.36 (s, 1H), 8.13 (m, 1H), 7.62 (m, 2H), 7.42 (t, 1H), 6.92 (dd, 1H), 3.80 (s, 3H), 2.85 (t, 2H), 1.76 (m, 2H), 0.94 (t, 3H) ppm.

d. 4-Chloro-1-(3-methoxyphenyl)-3-propyl-1*H*-pyrazolo[3,4-*d*]pyrimidine



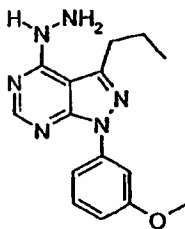
To a solution of 1-(3-methoxyphenyl)-3-propyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-ol (c, above) (2.32 g, 8.16 mmole) in phosphorous oxychloride (20 mL) was heated to reflux for 3 hours. The solution was cooled to RT and poured slowly over ice. The resulting mixture was extracted with methylene chloride (4 x 50 mL). The organics were dried (MgSO<sub>4</sub>) and concentrated to provide the product as a brown solid (2.70 g) that was used without further purification.

10

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.80 (s, 1H), 7.77 (m, 2H), 7.43 (t, 1H), 6.90 (dd, 1H), 3.90 (s, 3H), 3.15 (t, 2H), 1.90 (m, 2H), 1.09 (t, 3H) ppm.

15

e. 4-Hydrazino-1-(3-methoxyphenyl)-3-propyl-1*H*-pyrazolo[3,4-*d*]pyrimidine



To a solution of 4-chloro-1-(3-methoxyphenyl)-3-propyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (d, above) (2.70 g, 8.92 mmole) in ethanol (50 mL) was added hydrazine hydrate (1.70 mL, 54.6 mmole). The solution was heated to reflux for 3 hours, then was cooled to RT and concentrated. The residue was stirred with saturated aqueous sodium bicarbonate (50 mL) for 2 hours then filtered. The solid was washed with water and dried to provide the product as a tan solid (2.19 g, 82%).

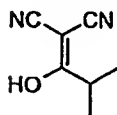
<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.50 (s, 1H), 7.71 (m, 2H), 7.37 (t, 1H), 6.83 (dd, 1H), 3.87 (s, 3H), 2.94 (t, 2H), 1.85 (m, 2H), 1.06 (t, 3H) ppm.

5

### Intermediates Example LL

#### 4-Hydrazino-3-isopropyl-1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine

- 10 a. 2-(1-Hydroxy-2-methylpropylidene)malononitrile

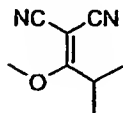


- To a suspension of sodium hydride (60% dispersion in mineral oil, 3.71 g, 92.8 mmole) in THF (50 mL) at 0°C was added a solution of malonitrile (2.90 mL, 46.1 mmole) in THF (10 mL) (gas evolution!). The resulting mixture was stirred for 15 minutes and
- 15 isobutyryl chloride (4.80 mL, 45.8 mmole) was added. The resulting solution was stirred at 0°C for 3 hours then at RT overnight. Sat. aq. potassium phosphate monobasic (100 mL) was added and the mixture was extracted with ethyl acetate (2 x 50 mL). The organic layers were dried (MgSO<sub>4</sub>) and concentrated to provide the product as a yellow solid that was carried on without further purification.

20

<sup>1</sup>H NMR (DMSO): δ 2.72 (m, 1H), 0.90 (d, 6H) ppm.

- b. 2-(1-Methoxy-2-methylpropylidene)malononitrile



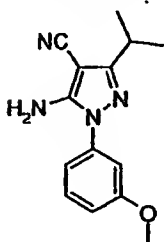
25

To a solution of 2-(1-hydroxy-2-methylpropylidene)malononitrile (a, above) in dioxane/water (6:1, 100 mL) was added solid sodium bicarbonate (19.374 g, 231

mmole) and dimethyl sulfate (20.0 mL, 211 mmole). The resulting mixture was heated to 80°C for 5 ½ hours. The mixture was cooled to RT and poured into brine (50 mL) and water (50 mL). The two layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 50 mL). The combined organic layers were dried (MgSO<sub>4</sub>) and concentrated. The residue obtained was dissolved in chloroform (100 mL) and filtered through a pad of celite. The resulting filtrate was concentrated to provide the product as a red oil (7.53 g, 63%).

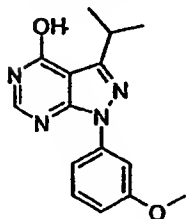
<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 4.35 (s, 3H), 3.16 (m, 1H), 1.16 (d, 6H) ppm.

c. 5-Amino-3-isopropyl-1-(3-methoxyphenyl)-1H-pyrazole-4-carbonitrile



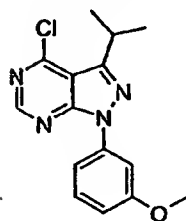
Prepared as described for 5-Amino-1-(3-methoxyphenyl)-3-propyl-1H-pyrazole-4-carbonitrile (Intermediates Example KK) from 2-(1-methoxy-2-methylpropylidene)malononitrile (b, above) (6.46 g, 43.0 mmole), 3-methoxyphenylhydrazine hydrochloride (7.53 g, 43.1 mmole) and triethylamine (12.0 mL, 86.1 mmole) in ethanol (100 mL) to provide the product as an orange oil (4.76 g, 43%).

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.38 (t, 1H), 7.04 (dd, 1H), 7.01 (m, 1H), 6.92 (dd, 1H), 4.61 (s, 2H), 3.83 (s, 3H), 3.04 (m, 1H), 1.34 (d, 6H) ppm.

**d. 3-Isopropyl-1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-ol**

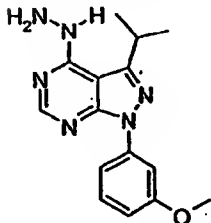
Prepared as described for 1-(3-methoxyphenyl)-3-propyl-1*H*-pyrazolo[3,4-  
5 *d*]pyrimidin-4-ol (Intermediates Example KK) from 5-amino-3-isopropyl-1-(3-methoxyphenyl)-1*H*-pyrazole-4-carbonitrile (c, above)(4.76 g, 18.6 mmole) in formic acid (100 mL) to provide the product as a white solid (2.92 g, 55%).

<sup>1</sup>H NMR (DMSO): δ 12.36 (s, 1H), 8.14 (d, 1H), 7.62 (m, 2H), 7.42 (t, 1H), 6.92 (dd, 1H),  
10 3.80 (s, 3H), 3.31 (m, 1H), 1.33 (d, 6H) ppm.

**e. 4-Chloro-3-isopropyl-1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine**

15 Prepared as described for 4-chloro-1-(3-methoxyphenyl)-3-propyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (Intermediates Example KK) from 3-isopropyl-1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-ol (2.92 g, 10.3 mmole) and phosphorous oxychloride (50 mL) to provide the product as a white solid (3.03 g, 97%).

20 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.79 (s, 1H), 7.81 (m, 2H), 7.43 (t, 1H), 6.89 (dd, 1H), 3.90 (s, 3H), 3.74 (m, 1H), 1.50 (d, 6H) ppm.

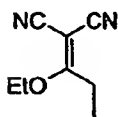
f. 4-Hydrazino-3-isopropyl-1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine

Prepared as described for 4-hydrazino-1-(3-methoxyphenyl)-3-propyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (Intermediates Example KK) from 4-chloro-3-isopropyl-1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (3.03 g, 10.0 mmole) and hydrazine hydrate (1.95 mL, 62.6 mmole) in ethanol (65 mL) to provide the product as a white solid (2.67 g, 90%).

<sup>1</sup>H NMR (DMSO): δ 8.36 (s, 1H), 7.81 (m, 1H), 7.76 (d, 1H), 7.40 (t, 1H), 6.86 (dd, 1H), 3.80 (s, 3H), 3.66 (m, 1H), 1.29 (d, 6H) ppm.

Intermediates Example MM4-Hydrazino-3-ethyl-1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine

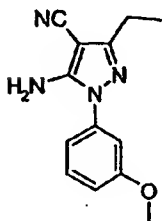
## b. 2-(1-Ethoxypropylidene)malononitrile



Prepared as described for 2-(1-ethoxybutylidene)malononitrile (Intermediates example KK) from malonitrile (6.30 mL, 100 mmole) and triethylorthopropionate (20.0 mL, 99.4 mmole) to provide the product as a yellow oil (15.832 g, 100%).

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 4.45 (q, 2H), 2.64 (q, 2H), 1.44 (t, 3H), 1.25 (t, 3H) ppm.

## c. 5-Amino-3-ethyl-1-(3-methoxyphenyl)-1H-pyrazole-4-carbonitrile

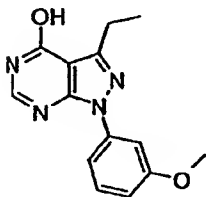


- 5 Prepared as described above for 5-amino-1-(3-methoxyphenyl)-3-propyl-1H-pyrazole-4-carbonitrile (Intermediates example KK) from 2-(1-ethoxypropylidene)malononitrile (2.584 g, 17.2 mmole) and 3-methoxyphenylhydrazine (2.998 g, 17.2 mmole) to provide the product as a yellow solid (1.85 g, 44%).

10

<sup>1</sup>H NMR (DMSO): δ 7.38 (t, 1H), 7.02 (d, 1H), 6.99 (m, 1H), 6.94 (dd, 1H), 6.63 (s, 2H), 3.79 (s, 3H), 2.51 (q, 2H), 1.18 (t, 3H) ppm.

## d. 1-(3-methoxyphenyl)-3-ethyl-1H-pyrazolo[3,4-d]pyrimidin-4-ol



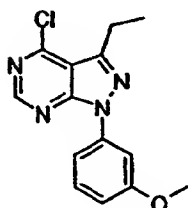
15

- Prepared as described for 1-(3-methoxyphenyl)-3-propyl-1H-pyrazolo[3,4-d]pyrimidin-4-ol (Intermediates Example KK) from 5-amino-3-ethyl-1-(3-methoxyphenyl)-1H-pyrazole-4-carbonitrile (c, above) (1.0 g, 4.13 mmole) in formic acid (40 mL) to provide the product as a white solid (0.9 g, 81%).

20

<sup>1</sup>H NMR (DMSO): δ 12.36 (s, 1H), 8.14 (s, 1H), 7.63 (m, 2H), 7.42 (t, 1H), 6.93 (dd, 1H), 3.80 (s, 3H), 2.89 (q, 2H), 1.29 (t, 3H) ppm.



e. 4-Chloro-3-ethyl-1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine

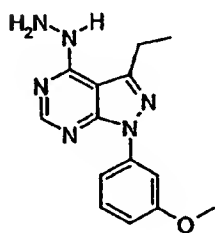
5

Prepared as described for 4-chloro-1-(3-methoxyphenyl)-3-propyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (Intermediates Example KK) from 3-ethyl-1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-ol (0.9 g, 3.3 mmole) and phosphorous oxychloride (3.7 mL) to provide the product as a white solid (913 mg, 95%).

10

<sup>1</sup>H NMR (DMSO): δ 8.92 (s, 1H), 7.74 (m, 2H), 7.49 (t, 1H), 6.98 (dd, 1H), 3.83 (s, 3H), 3.15 (q, 2H), 1.38 (t, 3H) ppm.

15

f. 4-Hydrazino-3-ethyl-1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine

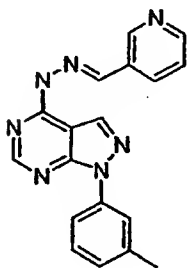
Prepared as described for 4-hydrazino-1-(3-methoxyphenyl)-3-propyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (Intermediates Example KK) from 4-chloro-3-ethyl-1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (913 mg, 3.12 mmole) and hydrazine hydrate (0.9 mL, 18.72 mmole) in ethanol (20 mL) to provide the product as a white solid (0.81 g, 91%).

<sup>1</sup>H NMR (DMSO): δ 8.37 (s, 1H), 7.78 (m, 2H), 7.40 (t, 1H), 6.86 (dd, 1H), 4.76 (broad s, 2H), 3.80 (s, 3H), 3.03 (q, 2H), 1.24 (t, 3H) ppm.

## EXAMPLES

### Example 1

Nicotinaldehyde [1-(3-methylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone



20

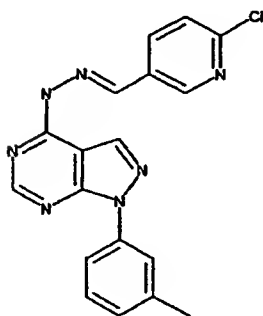
To a stirred solution of 4-hydrazino-1-(3-methylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (52 mg, 0.22 mmol) (Intermediates Example A) in ethanol (5 mL) was added nicotinaldehyde (28 mg, 0.26 mmol) and pyrrolidine. The resulting mixture was refluxed for ca. 3 hours, cooled to RT, and filtered to give the product as a white solid (30 mg, 41%).

<sup>1</sup>H NMR (DMSO) δ 12.39 (s, 1H), 8.91, (s, 1H), 8.64 (s, 1H), 8.62 (d, 1H), 8.50 (s, 1H), 8.33 (s, 1H), 8.30 (d, 1H), 8.03 (s, 1H), 7.99 (d, 1H), 7.52 (dd, 1H), 7.44 (t, 1H), 7.17 (d, 1H), 2.41 (s, 3H) ppm; ES-MS m/z 330 (MH<sup>+</sup>).

5

**Example 2**

**6-Chloronicotinaldehyde [1-(3-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone**



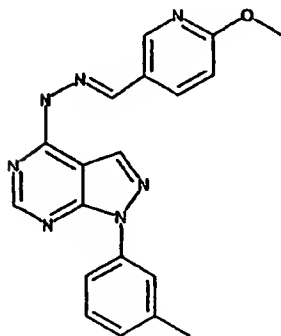
10

Prepared from 4-hydrazino-1-(3-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidine (Intermediates Example A) and 6-chloronicotinaldehyde using the general procedure for nicotinaldehyde [1-(3-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone (Example 1).

15

<sup>1</sup>H NMR (300 MHz, DMSO) δ 12.45 (s, 1H), 8.75 (d, 1H), 8.64 (s, 1H), 8.51 (s, 1H), 8.38 (dd, 1H), 8.32 (s, 1H), 8.02 (s, 1H), 7.99 (d, 1H), 7.61 (d, 1H), 7.43 (t, 1H), 7.18 (d, 1H), 2.40 (s, 3H) ppm.

20

**Example 3****6-Methoxynicotinaldehyde [1-(3-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone**

5

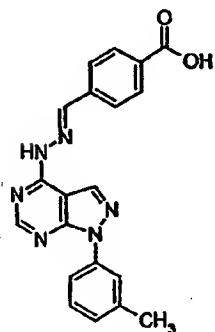
- 10 A mixture of 6-chloronicotinaldehyde [1-(3-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone (0.075 g; 0.21 mmol) (Example 2) and sodium methoxide (0.080 g; 1.51 mmol) in DMSO (3 mL) were heated to 105 °C for 1h. The solution was cooled to RT then water (25 mL) and 1N HCl (15 mL) were added. The solid was filtered, washed with MeOH (3 mL) then Et<sub>2</sub>O (5 mL) and dried to give title compound
- 15 (34 mg) as a off-white powder (45%).

<sup>1</sup>H NMR (300 MHz, DMSO) δ 12.29 (s, 1H), 8.67 (s, 1H), 8.51 (s, 2H), 8.36-8.33 (m, 2H), 8.07-8.02 (m, 2H), 7.48 (t, 1H), 7.22 (d, 1H), 7.00 (d, 1H), 3.95 (s, 3H), 2.56 (s, 3H) ppm.

20

**Example 4**

4-((*E*)-{[1-(3-methylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]  
hydrazono}methyl)benzoic acid

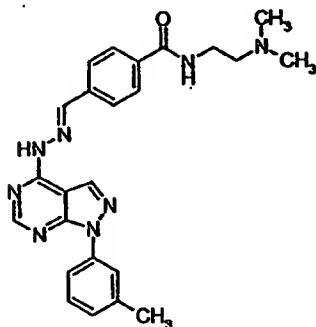


Prepared from 4-hydrazino-1-(3-methylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine  
10 (Intermediates Example A) and 4-formylbenzoic acid using the general procedure for  
nicotinaldehyde [1-(3-methylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone  
(Example 1).

<sup>1</sup>H NMR (300 MHz, DMSO) δ 13.26–12.10 (m br, 2H), 8.67 (s, 1H), 8.53 (s, 1H), 8.37 (s,  
15 1H), 8.10–7.99 (m, 4H), 7.97–7.94 (m, 1H), 7.46 (t, 1H), 7.21 (d, 2H), 2.43 (s, 3H) ppm;  
ES-MS *m/z* 373 (MH<sup>+</sup>).

**Example 5**

*N*-[2-(Dimethylamino)ethyl]-4-((*E*)-{[1-(3-methylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazono}methyl)benzamide



5

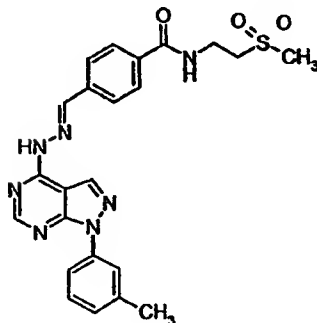
To a solution of 4-((*E*)-{[1-(3-methylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazono}methyl)benzoic acid (Example 4) (45 mg, 0.120 mmol) in DMF (4 mL),  
 10 was added *N,N*-dimethylethane-1,2-diamine (0.02 mL, 0.180 mmol),  
 diethylcyanophosphonate (0.036 mL, 0.240 mmol), and triethylamine (0.05 mL, 0.360 mmol). The solution was stirred at rt for 1 h, then water and diethyl ether were added. The resulting precipitate was collected by filtration to give pure product (18 mg, yield 34%).

15

<sup>1</sup>H NMR (300 MHz, DMSO) δ 12.34 (s, 1H), 8.66 (s, 1H), 8.54-8.48 (m, 2H), 8.35 (s, 1H), 8.09-7.84 (m, 6H), 7.45 (t, 1H), 7.20 (d, 1H), 3.46-3.32 (m, 2H), 2.55-2.50 (m, 2H), 2.42 (s, 3H), 2.23 (s, 6H) ppm; ES-MS *m/z* 443 (MH<sup>+</sup>).

**Example 6**

4-((*E*)-{[1-(3-Methylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]  
hydrazono}methyl)-*N*-[2-(methylsulfonyl)ethyl]benzamide



5

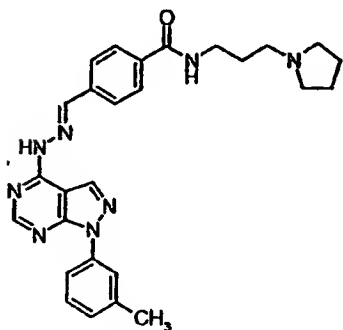
To a solution of 4-((*E*)-{[1-(3-methylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-  
yl]hydrazono}methyl)benzoic acid (Example 4) (45 mg, 0.12 mmol) in DMF (4 mL), was  
10 added 2-(methylsulfonyl)ethanamine hydrochloride (29 mg, 0.180 mmol),  
diethylcyanophosphonate (0.036 mL, 0.240 mmol), and triethylamine (0.05 mL, 0.360  
mmol). The solution was stirred at rt for ca.16 h, then water and diethyl ether were  
added. The resulting precipitate was collected by filtration to give pure product (48  
15 mg, yield 84%).

<sup>1</sup>H NMR (300 MHz, DMSO) δ 12.37 (s, 1H), 8.83 (t, 1H), 8.68 (s, 1H), 8.52 (s, 1H), 8.35 (s,  
1H), 8.09-7.96 (m, 2H), 7.94 (s, 4H), 7.46 (t, 1H), 7.24-7.19 (m, 1H), 3.70 (q, 2H), 3.41 (q,  
2H), 3.05 (s, 3H), 2.42 (s, 3H) ppm; ES-MS *m/z* 478 (MH<sup>+</sup>).

20

**Example 7**

4-((*E*)-{[1-(3-methylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazono}methyl)-*N*-(3-pyrrolidin-1-ylpropyl)benzamide



5

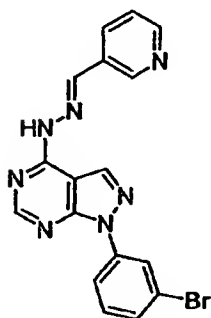
To a solution of 4-((*E*)-{[1-(3-methylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazono}methyl)benzoic acid (Example 4) (45 mg, 0.12 mmol) in DMF (4 mL), was added 3-pyrrolidin-1-ylpropan-1-amine (29 mg, 0.180 mmol), diethylcyanophosphonate (0.036 mL, 0.240 mmol), and triethylamine (0.05 mL, 0.360 mmol). The solution was stirred at rt for 3 h, then water and diethyl ether were added. The resulting precipitate was collected by filtration to give pure product (5 mg, yield 9%).

15

<sup>1</sup>H NMR (300 MHz, DMSO) δ 12.36 (s, 1H), 8.69-8.62 (m, 2H), 8.52 (s, 1H), 8.35 (s, 1H), 8.09-8.00 (m, 2H), 7.99-7.88 (m, 4H), 7.46 (t, 1H), 7.25-7.18 (m, 1H), 3.40-3.25 (m, 2H), 2.55-2.44 (m, 6H), 2.42 (s, 3H), 1.75-1.63 (m, 6H) ppm. ES-MS *m/z* 483 (MH<sup>+</sup>).

20



**Example 8****Nicotinaldehyde [1-(3-bromophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone**

5

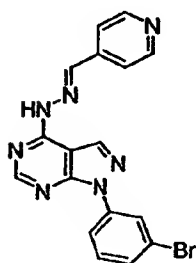
Nicotinaldehyde (0.031 mL, 0.33 mmol) and two drops of pyrrolidine were added to a suspension of 1-(3-bromophenyl)-4-hydrazino-1H-pyrazolo[3,4-d]pyrimidine hydrochloride (Intermediates Example B) (0.095 g, 0.28 mmol) in 15 mL of absolute ethanol. The mixture was heated at reflux for 3 hours. After cooling to room temperature, diethyl ether was added and the precipitated solid was collected by filtration and dried under vacuum to give 0.081 g (67%) of product as a white solid.

<sup>1</sup>H NMR (DMSO) δ 8.90 (s, 1H), 8.70 (s, 1H), 8.65 (m, 1H), 8.55 (m, 2H), 8.35 (s, 1H), 8.30 (dd, 2H), 7.50 (m, 4H) ppm; ES-MS m/z 394 (M<sup>+</sup>), 396 (M+2).

15

**Example 9****Isonicotinaldehyde [1-(3-bromophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone**

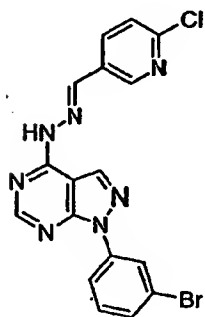
5



4-Hydrazino-1-(3-bromophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine hydrochloride

10 (Intermediates Example B) (0.070 g, 0.23 mmol) was treated with isonicotinaldehyde (0.073 g, 0.68 mmol) in absolute ethanol as described for nicotinaldehyde [1-(3-methylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone (Example 1) to give 66 mg (73%) of product as an off-white solid.

15 <sup>1</sup>H NMR (DMSO) δ 12.60 (br s, 1H), 8.70 (s, 1H), 8.67 (d, 2H), 8.55 (d, 2H), 8.26 (m, 2H), 7.79 (d, 2H), 7.54 (m, 2H) ppm; ES-MS *m/z* 396 (M+2)

**Example 10****6-Chloronicotinaldehyde [1-(3-bromophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone**

5

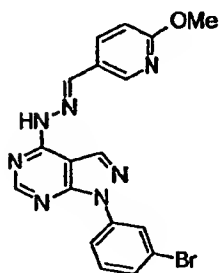
A mixture of 1-(3-bromophenyl)-4-hydrazino-1H-pyrazolo[3,4-d]pyrimidine hydrochloride (Intermediates Example B) (0.100 g, 0.33 mmol), 6-chloronicotinaldehyde (0.046 g, 0.33 mmol), and 10 mL of absolute ethanol was heated at reflux for 18 hours. After cooling to room temperature, the solid product was collected by filtration, washed with ethanol and dried under vacuum to give 0.115 g (82%) of a yellow powder.

15

<sup>1</sup>H NMR (DMSO) δ 12.50 (br s, 1H), 8.75 (s, 1H), 8.70 (s, 1H), 8.55 (d, 2H), 8.40 (d, 1H), 8.30 (s, 1H), 8.25 (d, 1H), 7.65 (d, 1H), 7.55 (m, 2H) ppm.

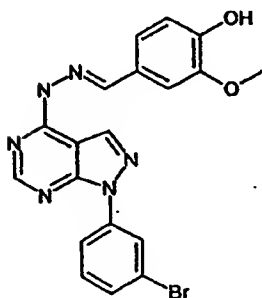
**Example 11****6-Methoxynicotinaldehyde [1-(3-bromophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone**

5



Sodium methoxide (0.086 g, 1.59 mmol) was added to a suspension of 6-chloronicotinaldehyde [1-(3-bromophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone (Example 10) (0.114 g, 0.27 mmol) in 5 mL of dimethyl sulfoxide. The mixture was heated to 100°C for two hours resulting in a homogeneous solution. After cooling to room temperature, water (5 mL) was added and the precipitated solid was collected by filtration, washed with water, methanol and diethyl ether and dried under vacuum for two hours to give 73 mg (64%) of a tan solid.

<sup>1</sup>H-NMR (DMSO) δ 12.30 (br s, 1H), 8.64 (s, 1H), 8.51 (d, 2H), 8.45 (s, 1H), 8.26 (m, 3H), 7.52 (m, 2H), 6.93 (d, 1H), 3.90 (s, 3H) ppm; ES-MS m/z 424 (M), 426 (M+2)

**Example 12****4-Hydroxy-3-methoxybenzaldehyde [1-(3-bromophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone**

5

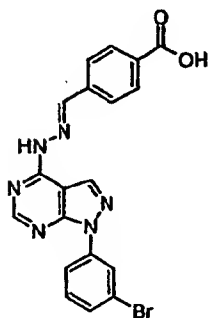
Prepared from 1-(3-bromophenyl)-4-hydrazino-1H-pyrazolo[3,4-d]pyrimidine  
10 (Intermediates Example B) and 4-hydroxy-3-methoxybenzaldehyde using the general  
procedure for nicotinaldehyde [1-(3-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-  
yl]hydrazone (Example 1).

<sup>1</sup>H NMR (400 MHz, DMSO) δ 8.58 (s, 1H), 8.52 (s, 1H), 8.45 (s, 1H), 8.26 (d, 1H), 8.17 (s,  
15 1H), 7.48-7.51 (m, 2H), 7.32 (s, 1H), 7.19 (d, 1H), 6.85 (d, 1H), 3.86 (s, 3H) ppm. ES-MS  
m/z 440 (MH<sup>+</sup>)

**Example 13**

4-((E)-{[1-(3-Bromophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazono}methyl)benzoic acid

5



10

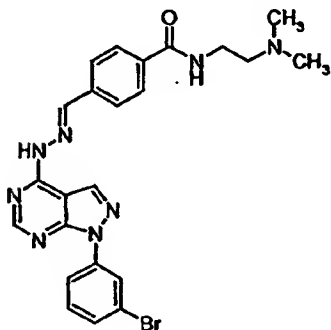
Prepared from 4-Hydrazino-1-(3-bromophenyl)-1H-pyrazolo[3,4-d]pyrimidine hydrochloride (Intermediates Example B) and 4-formylbenzoic acid using the general procedure for nicotinaldehyde [1-(3-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone (Example 1).

15

<sup>1</sup>H NMR (300 MHz, DMSO) δ 13.27-12.37 (m br, 2H), 8.71 (s, 1H), 8.57 (s, 2H), 8.37 (s, 1H), 8.32-7.24 (m, 1H), 8.04 (d, 2H), 7.95 (d, 2H), 7.60-7.48 (m, 2H) ppm; ES-MS m/z 439 (MH<sup>+</sup>).

**Example 14**

4-((E)-{[1-(3-bromophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazono}methyl)-N-[2-(dimethylamino)ethyl]benzamide



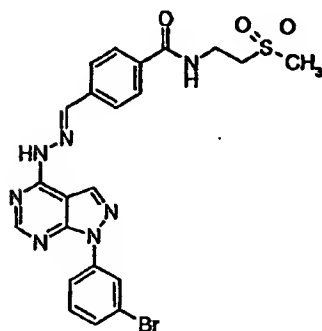
To a solution of 4-((E)-{[1-(3-bromophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazono}methyl)benzoic acid (Example 13) (45 mg, 0.120 mmol) in DMF (4 mL),  
10 was added N,N-dimethylethane-1,2-diamine (0.02 mL, 0.180 mmol),  
diethylcyanophosphonate (0.036 mL, 0.240 mmol), and triethylamine (0.05 mL, 0.360 mmol). The solution was stirred at rt for 1 h, then water and diethyl ether were added. The resulting precipitate was collected by filtration to give pure product (37  
15 mg, yield 61%).

<sup>1</sup>H NMR (300 MHz, DMSO) δ 12.44 (s, 1H), 8.69 (s, 1H), 8.65–8.52 (m, 2H), 8.35 (s, 1H), 8.33–8.22 (m, 1H), 8.10–7.85 (m, 5H), 7.59–7.50 (m, 2H), 3.46–3.32 (m, 2H), 2.62–2.50 (m, 2H), 2.30 (s, 6H) ppm; ES-MS m/z 509 (MH<sup>+</sup>).

**Example 15**

4-((*E*)-{[1-(3-Bromophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazono}methyl)-*N*-(2-(methylsulfonyl)ethyl)benzamide

5



10

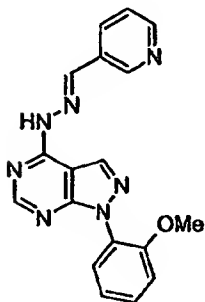
To a solution of 4-((*E*)-{[1-(3-bromophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazono}methyl)benzoic acid (Example 13) (53 mg, 0.12 mmol) in DMF (4 mL), was added 2-(methylsulfonyl)ethanamine hydrochloride (29 mg, 0.180 mmol), diethylcyanophosphonate (0.036 mL, 0.240 mmol), and triethylamine (0.05 mL, 0.360 mmol). The solution was stirred at rt for 16 h, then water and diethyl ether were added. The resulting precipitate was collected by filtration to give pure product (45 mg, yield 69%).

15

<sup>1</sup>H NMR (300 MHz, DMSO) δ 12.44 (s, 1H), 8.84 (t, 1H), 8.72 (s, 1H), 8.56 (s, 1H), 8.36 (s, 1H), 8.33-8.26 (m, 1H), 7.94 (s, 5H), 7.59-7.53 (m, 2H), 3.71 (q, 2H), 3.42 (q, 2H), 3.05 (s, 3H) ppm; ES-MS *m/z* 544 (MH<sup>+</sup>).

20



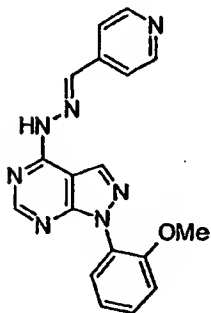
**Example 16****Nicotinaldehyde [1-(2-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone**

5

4-Hydrazino-1-(2-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine hydrochloride (Intermediates Example C) (0.0647 g, 0.22 mmol) was treated with nicotinaldehyde (0.025 mL, 0.26 mmol) in absolute ethanol as described for nicotinaldehyde [1-(3-methylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone (Example 1) to give 0.051 g (61%) of product as an off-white solid.

<sup>1</sup>H NMR (DMSO) δ 12.30 (br s, 1H), 8.90 (s, 1H), 8.60 (m, 2H), 8.30 (m, 3H), 7.50 (m, 2H), 7.40 (d, 1H), 7.30 (d, 1H), 7.10 (t, 1H), 3.70 (s, 3H) ppm. ES-MS *m/z* 346 (MH<sup>+</sup>)

15

Example 17Isonicotinaldehyde [1-(2-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone

5

4-Hydrazino-1-(2-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine hydrochloride

(Intermediates Example C) (0.070 g, 0.24 mmol) was treated with isonicotinaldehyde

10 (0.068 mL, 0.72 mmol) as described for nicotinaldehyde [1-(3-methylphenyl)-1H-

pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone (Example 1) to give 0.0335 g of product as a light yellow solid.

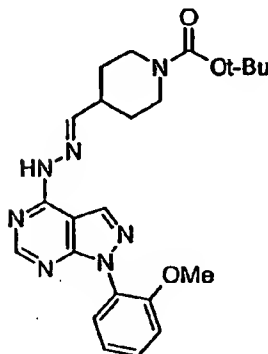
<sup>1</sup>H NMR (400 MHz, DMSO) δ 12.40 (br s, 1H), 8.67 (d, 2H), 8.60 (s, 1H), 8.36 (s, 1H), 8.25

15 (s, 1H), 7.77 (d, 2H), 7.53 (t, 1H), 7.41 (dd, 1H), 7.25 (d, 1H), 7.11 (t, 1H), 3.75 (s, 3H)

ppm; ES-MS m/z 345 (MH<sup>+</sup>)

**Example 18**

*tert*-Butyl 4-(((*E*)-{[1-(2-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazono}methyl)piperidine-1-carboxylate

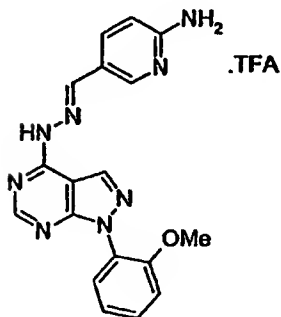


5

- 4-Hydrazino-1-(2-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine hydrochloride (Intermediates Example C) (0.070 g, 0.24 mmol) was treated with *tert*-butyl 4-formylpiperidine-1-carboxylate (0.102 g, 0.48 mmol) and one drop of pyrrolidine in 7 mL of absolute ethanol as described for isonicotinaldehyde [1-(2-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone (Example 17). The solvent was removed under vacuum and the crude product was purified by flash chromatography on silica gel with dichloromethane:methanol/95:5 to give 49 mg (45%) of pure product.

<sup>1</sup>H NMR (DMSO) δ 11.75 (br s, 1H), 8.33 (s, 1H), 8.22 (s, 1H), 7.57 (d, 1H), 7.51 (t, 1H), 7.37 (d, 1H), 7.24 (d, 1H), 7.09 (t, 1H), 3.97 (d, 2H), 3.68 (s, 3H), 2.90 (br m, 2H), 2.50 (m, 2H), 1.89 (d, 2H), 1.38 (s, 9H) ppm; APCI-MS *m/z* 451 (MH<sup>+</sup>)

20

**Example 19****6-Aminonicotinaldehyde [1-(2-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone trifluoroacetate**

5

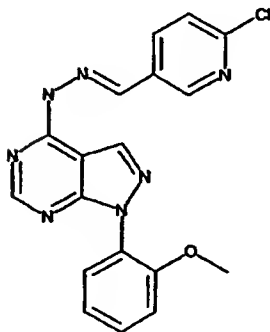
- A mixture of 4-hydrazino-1-(2-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine hydrochloride (Intermediates Example C) (0.070 g, 0.24 mmol), *tert*-butyl 5-formylpyridin-2-ylcarbamate (0.106 g, 0.48 mmol), a drop of pyrrolidine, and 7 mL of absolute ethanol was heated at reflux for 6 hours. The cooled reaction mixture was filtered. The collected solid was washed with ethanol, dried under vacuum and treated with 1 mL of trifluoroacetic acid at room temperature for 30 minutes, then evaporated to dryness. The residue was taken up in methanol and the mixture filtered.
- The filtrate was evaporated and the residue purified by reverse phase HPLC (C18 column with 5-50% acetonitrile/water/0.1% formic acid gradient) to give 5 mg of pure product.

- <sup>1</sup>H NMR (DMSO) δ 8.58 (d, 1H), 8.52 (dd, 1H), 8.30 (m, 2H), 8.19 (s, 1H), 7.53 (t, 1H), 7.40 (dd, 1H), 7.26 (d, 1H), 7.10 (m, 2H), 5.40 (br s, 2H), 3.70 (s, 3H) ppm; ES-MS *m/z* 361 (MH<sup>+</sup>)

20

**Example 20**

**6-chloronicotinaldehyde [1-(2-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone**



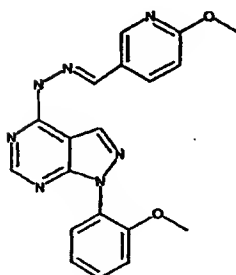
5

Prepared from 4-Hydrazino-1-(2-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine hydrochloride (Intermediates Example C) and 6-chloronicotinaldehyde using the  
10 general procedure for nicotinaldehyde [1-(3-methylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone (Example 1).

<sup>1</sup>H NMR (300 MHz, DMSO) δ 12.37 (s, 1H), 8.75 (s, 1H), 8.58 (s, 1H), 8.38 (d, 1H), 8.33 (s, 1H), 8.31 (s, 1H), 7.61 (d, 1H), 7.53 (t, 1H), 7.40 (d, 1H), 7.26 (d, 1H), 7.11 (t, 1H), 3.70 (s,  
15 3H) ppm.

**Example 21****6-Methoxynicotinaldehyde [1-(2-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone**

5



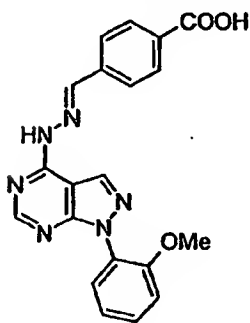
10 A mixture of 6-chloronicotinaldehyde [1-(2-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone (Example 20) (0.075 g; 0.20 mmol) and sodium methoxide (0.080 g; 1.51 mmol) in DMSO (3 mL) were heated to 105 °C for 1h. The solution was cooled to RT then water (25 mL) and 1N HCl (15 mL) were added. The solid was filtered, washed with MeOH (3 mL) then Et<sub>2</sub>O (5 mL) and dried to give title compound (41 mg) as a off-white powder (55%).

15

<sup>1</sup>H NMR (300 MHz, DMSO) δ 12.30 (s, 1H), 8.59 (s, 1H), 8.51 (d, 1H), 8.39–8.31 (m, 3H), 7.56 (t, 1H), 7.45 (d, 1H), 7.30 (d, 1H), 7.15 (t, 1H), 6.99 (d, 1H), 3.94 (s, 3H), 3.74 (s, 3H) ppm.

**Example 22**

**4-((E)-{[1-(2-Methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazono}methyl)benzoic acid**



5

4-Hydrazino-1-(2-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine hydrochloride

(Intermediates Example C) (0.070 g, 0.24 mmol) was treated with 4-

carboxybenzaldehyde (0.108 g, 0.72 mmol) as described for nicotinaldehyde [1-(3-

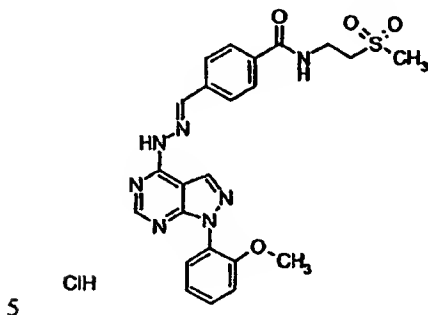
10 methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone (Example 1). The crude solid product was triturated with methanol and dried under vacuum to give 14 mg (15%) of pure product as a light yellow solid.

<sup>1</sup>H NMR (DMSO) δ 8.60 (s, 1H), 8.34 (d, 2H), 8.04 (s, 1H), 8.02 (d, 2H), 7.93 (d, 2H), 7.53

15 (t, 1H), 7.42 (d, 1H), 7.26 (d, 1H), 7.11 (t, 1H), 3.75 (s, 3H) ppm; APCI-MS m/z 388 (MH<sup>+</sup>).

**Example 23**

**4-((*E*)-{[1-(2-Methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazono} methyl)-*N*-(2-(methylsulfonyl)ethyl)benzamide hydrochloride**



To a solution of 4-((*E*)-{[1-(2-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazono} methyl)benzoic acid (Example 22) (47 mg, 0.12 mmol) in DMF (4 mL),  
 10 was added 2-(methylsulfonyl)ethanamine hydrochloride (29 mg, 0.180 mmol), diethylcyanophosphonate (0.036 mL, 0.240 mmol), and triethylamine (0.05 mL, 0.360 mmol). The solution was stirred at rt for 16 h, then partitioned between water and diethyl ether. The aqueous layer was made acidic with 1N HCl, then concentrated.  
 15 The resulting solid was washed with ethanol and diethyl ether, and collected by filtration to give pure product (48 mg, yield 81%).

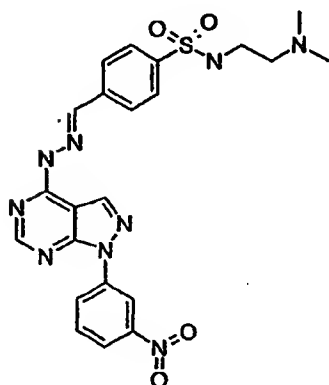
<sup>1</sup>H NMR (300 MHz, DMSO) δ 12.83-12.08 (s br, 1H), 8.89-8.83 (m, 1H), 8.62 (s, 1H), 8.35 (s, 1H), 8.35 (s, 1H), 7.94 (s, 4H), 7.90-7.82 (m, 2H), 7.48 (t, 1H), 6.99-6.92 (m, 1H),  
 20 3.84 (s, 3H), 3.71 (q, 2H), 3.42 (q, 2H), 3.05 (s, 3H) ppm; ES-MS *m/z* 494 (MH<sup>+</sup>).



**Example 24**

*N*-[2-(Dimethylamino)ethyl]-4-((*E*)-{[1-(3-nitrophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazono}methyl)benzenesulfonamide

5



The title compound was prepared according to the general procedure for  
10 nicotinaldehyde [1-(3-methylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone  
(Example 1)  
from 4-hydrazino-1-(3-nitrophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine hydrochloride  
(Intermediates Example D) (65 mg, 0.21 mmol) and *N*-[2-(dimethylamino)ethyl]-4-  
formylbenzenesulfonamide (Intermediates Example U) (162 mg, 0.063 mmol) to give  
15 the product as a white solid (81 mg, 76%).

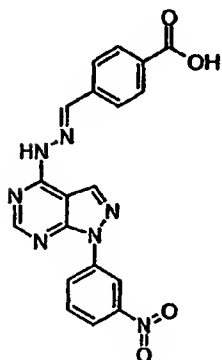
<sup>1</sup>H NMR (DMSO) 12.58 (s, 1H), 10.11 (s, 1H), 9.22 (t, 1H), 8.75 (s, 1H), 8.62 (s, 1H), 8.39  
(s, 1H), 8.19 (m, 2H), 8.07 (d, 2H), 7.94 (d, 2H), 7.88 (t, 1H), 3.15 (s, 4H), 2.76 (s, 6H) δ  
ppm; ES-MS *m/z* 510 (MH<sup>+</sup>).

20

Example 25

4-((E)-{[1-(3-Nitrophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazono}methyl)benzoic acid

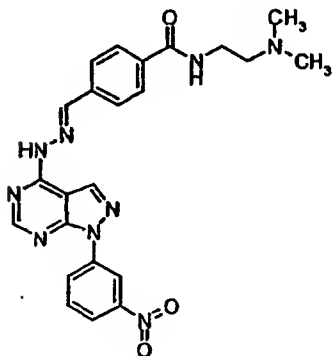
5



- 10 Prepared from 4-hydrazino-1-(3-nitrophenyl)-1H-pyrazolo[3,4-d]pyrimidine hydrochloride (Intermediates Example D) and 4-formylbenzoic acid using the general procedure for nicotinaldehyde [1-(3-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone (Example 1).
- 15 <sup>1</sup>H NMR (300 MHz, DMSO) δ 12.67-12.31 (s br, 1H), 9.23 (s, 1H), 8.80-8.72 (m, 2H), 8.61 (s, 1H), 8.37 (s, 1H), 8.24-8.18 (m, 1H), 8.08-8.00 (m, 2H), 7.98-7.84 (m, 3H) ppm.

**Example 26**

*N*-[2-(Dimethylamino)ethyl]-4-((*E*-{[1-(3-nitrophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazono}methyl)benzamide



5

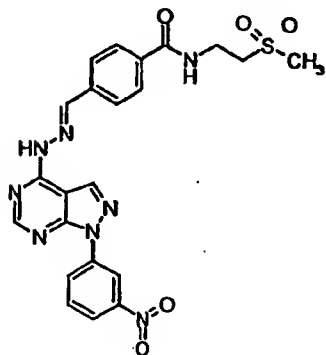
To a solution of 4-((*E*-{[1-(3-nitrophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazono}methyl)benzoic acid (Example 25) (39 mg, 0.10 mmol) in DMF (4 mL),  
 10 was added *N,N*-dimethylethane-1,2-diamine (0.02 mL, 0.180 mmol),  
 diethylcyanophosphonate (0.036 mL, 0.240 mmol), and triethylamine (0.05 mL, 0.360 mmol). The solution was stirred at rt for 1 h, then water and diethyl ether were added. The resulting precipitate was collected by filtration to give pure product (23 mg, yield  
 15 40%).

<sup>1</sup>H NMR (300 MHz, DMSO) δ 12.46 (s, 1H), 9.23 (s, 1H), 8.80-8.72 (m, 2H), 8.60 (s, 1H), 8.58-8.50 (m, 1H), 8.36 (s, 1H), 8.26-8.15 (m, 1H), 7.98-7.84 (m, 5H), 3.46-3.32 (m, 2H), 2.62-2.50 (m, 2H), 2.25 (s, 6H) ppm; ES-MS *m/z* 474 (MH<sup>+</sup>).

20

**Example 27**

*N*-[2-(Methylsulfonyl)ethyl]-4-((*E*)-{[1-(3-nitrophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazono}methyl)benzamide

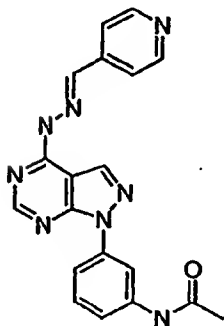


To a solution of 4-((*E*)-{[1-(3-nitrophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazono}methyl)benzoic acid (Example 25) (48 mg, 0.12 mmol) in DMF (4 mL),  
10 was added 2-(methylsulfonyl)ethanamine hydrochloride (29 mg, 0.180 mmol), diethylcyanophosphonate (0.036 mL, 0.240 mmol), and triethylamine (0.05 mL, 0.360 mmol). The solution was stirred at rt for 16 h, then water and diethyl ether were added. The resulting precipitate was collected by filtration to give pure product (49  
15 mg, yield 80%).

<sup>1</sup>H NMR (300 MHz, DMSO) δ 12.45 (s, 1H), 9.22 (s, 1H), 8.84 (t, 1H), 8.78-8.70 (m, 2H), 8.60 (s, 1H), 8.35 (s, 1H), 8.21-8.16 (m, 1H), 7.94 (s, 4H), 7.92-7.83 (m, 1H), 3.70 (q, 2H), 3.46-3.38 (m, 2H), 3.05 (s, 3H) ppm; ES-MS *m/z* 509 (MH<sup>+</sup>).

**Example 28**

*N*-[3-{4-[(2*E*-2-(pyridin-4-ylmethylene)hydrazino]-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl}phenyl)acetamide



The title compound was prepared according to the general procedure for  
10 nicotinaldehyde [1-(3-methylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone  
(Example 1) from *N*-[3-(4-hydrazino-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-  
yl)phenyl]acetamide hydrochloride (Intermediates Example E) (80 mg, 0.25 mmol) and  
isonicotinaldehyde (90 mg, 0.85 mmol) to give the product as a white solid (53 mg,  
57%).

15

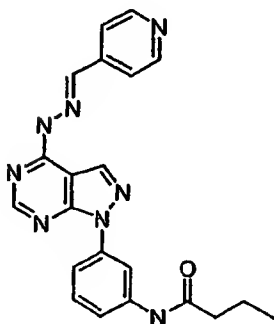
<sup>1</sup>H NMR (DMSO) δ 12.52 (s, 1H), 10.19 (s, 1H), 8.69 (m, 3H), 8.52 (d, 2H), 8.28 (s, 1H),  
7.93 (d, 1H), 7.80 (d, 2H), 7.57 (d, 1H), 7.47 (t, 1H), 2.08 (s, 3H) ppm. ES-MS *m/z* 373  
(MH<sup>+</sup>).

20

**Example 29**

*N*-[3-{4-[(2*E*)-2-(pyridin-4-ylmethylene)hydrazino]-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl}phenyl]butanamide

5



- 10 Title compound was prepared according to the general procedure for nicotinaldehyde [1-(3-methylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone (Example 1) from *N*-[3-(4-hydrazino-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)phenyl]butanamide hydrochloride (Intermediates Example F) (100 mg, 0.25 mmol) and isonicotinaldehyde (100 mg, 0.94 mmol) to give the product as a pale yellow solid (95 mg, 95%).

15

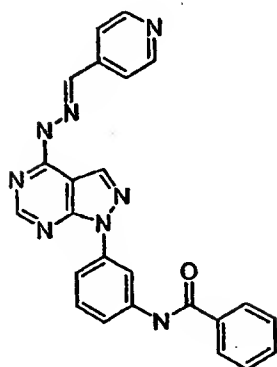
<sup>1</sup>H NMR (DMSO) δ 12.51 (s, 1H), 10.12 (s, 1H), 8.68 (m, 3H), 8.51 (d, 2H), 8.29 (s, 1H), 7.92 (d, 1H), 7.79 (d, 2H), 7.60 (d, 1H), 7.47 (t, 1H), 2.33 (t, 2H), 1.63 (m, 2H), 0.93 (t, 3H) ppm; ES-MS *m/z* 401(MH<sup>+</sup>).

20

**Example 30**

*N*-[3-{4-[(2*E*)-2-(pyridin-4-ylmethylene)hydrazino]-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl}phenyl]benzamide

118



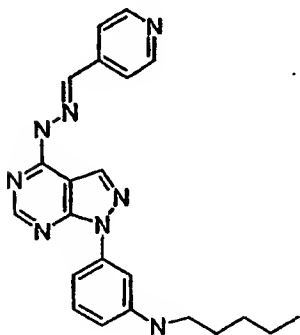
- 5 The title compound was prepared according to the general procedure for nicotinaldehyde [1-(3-methylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone (Example 1) from *N*-[3-(4-hydrazino-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)phenyl]benzamide hydrochloride (Intermediates Example G) (65 mg, 0.17 mmol) and isonicotinaldehyde (100 mg, 0.94 mmol) to give the product as a white solid (35  
10 mg, 47%).

<sup>1</sup>H NMR (DMSO) δ 12.52 (s, 1H), 10.51 (s, 1H), 8.69 (m, 4H), 8.56 (s, 1H), 8.29 (s, 1H), 8.01 (m, 3H), 7.79 (m, 3H), 7.59 (m, 4H) ppm; ES-MS *m/z* 435 (MH<sup>+</sup>).

15

**Example 31**

**Isonicotinaldehyde {1-[3-(pentylamino)phenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl}hydrazone**



5

The title compound was prepared according to the general procedure for  
10 isonicotinaldehyde [1-(2-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone  
(Example 17) from 3-(4-hydrazino-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-*N*-pentylaniline  
hydrochloride (Intermediates Example H) (42 mg, 0.12 mmol) and isonicotinaldehyde  
(50 mg, 0.47 mmol) to give impure product as a green solid. The crude product was  
purified by silica gel chromatography (3% methanol in methylene chloride) to give the  
15 pure product (21 mg, 44 %).

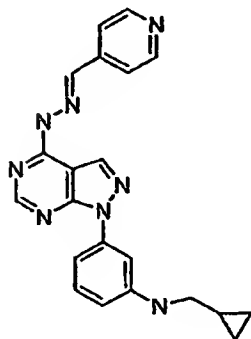
<sup>1</sup>H NMR (DMSO) δ 12.47 (s, 1H), 8.67 (m, 3H), 8.51 (s, 1H), 8.27 (s, 1H), 7.79 (d, 2H),  
7.37 (d, 2H), 7.21 (t, 1H), 6.55 (d, 1H), 5.94 (t, 1H), 3.04 (q, 2H), 1.59 (t, 2H), 1.34 (brs,  
4H), 0.89 (t, 3H) ppm; ES-MS *m/z* 401 (MH<sup>+</sup>).

20



**Example 32**

**Isonicotinaldehyde (1-{3-[(cyclopropylmethyl)amino]phenyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)hydrazone**



5

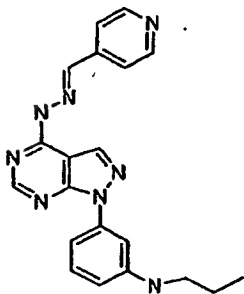
The title compound was prepared according to the general procedure for nicotinaldehyde [1-(3-methylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone

- 10 (Example 1) from *N*-(cyclopropylmethyl)-3-(4-hydrazino-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)aniline hydrochloride (Intermediates Example I) (48 mg, 0.14 mmol) and isonicotinaldehyde (55 mg, 0.52 mmol) to give the product as a tan solid (37 mg, 69%).

- 15 <sup>1</sup>H NMR (DMSO) δ 12.47 (s, 1H), 8.67 (m, 3H), 8.52 (s, 1H), 8.27 (s, 1H), 7.79 (d, 2H), 7.40 (d, 2H), 7.22 (t, 1H), 6.58 (d, 1H), 6.05 (brs, 1H), 2.95 (t, 2H), 1.07 (m, 1H), 0.48 (dd, 2H), 0.24 (dd, 2H) ppm; ES-MS *m/z* 385 (MH<sup>+</sup>).

Example 33

Isonicotinaldehyde {1-[3-(propylamino)phenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl} hydrazone

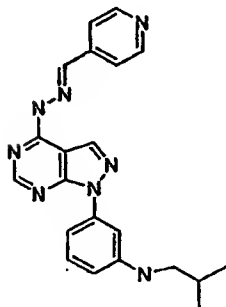


The title compound was prepared according to the general procedure for  
10 nicotinaldehyde [1-(3-methylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone  
(Example 1) from 3-(4-hydrazino-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-*N*-propylaniline  
hydrochloride (Intermediates Example J) (51 mg, 0.16 mmol) and isonicotinaldehyde  
(55 mg, 0.52 mmol) to give the product as a tan solid (41 mg, 69%).

15 <sup>1</sup>H NMR (DMSO) δ 12.48 (s, 1H), 8.67 (m, 3H), 8.51 (s, 1H), 8.27 (s, 1H), 7.79 (d, 2H),  
7.37 (d, 2H), 7.22 (t, 1H), 6.55 (d, 1H), 5.96 (brs, 1H), 3.02 (brs, 2H), 1.60 (m, 2H), 0.96  
(t, 3H) ppm; ES-MS *m/z* 373 (MH<sup>+</sup>).

**Example 34**

**Isonicotinaldehyde {1-[3-(isobutylamino)phenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl}hydrazone**



5

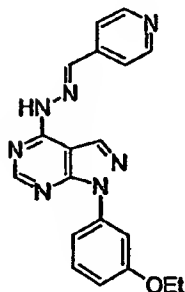
The title compound was prepared according to the general procedure for nicotinaldehyde [1-(3-methylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone (Example 1) from 3-(4-hydrazino-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-*N*-isobutylaniline hydrochloride (Intermediates Example K) (60 mg, 0.18 mmol) and isonicotinaldehyde (60 mg, 0.57 mmol) to give the product as a tan solid (44 mg, 63%).

<sup>1</sup>H NMR (DMSO) δ 12.47 (s, 1H), 8.67 (m, 3H), 8.51 (s, 1H), 8.27 (s, 1H), 7.79 (d, 2H), 7.37 (d, 2H), 7.21 (t, 1H), 6.56 (d, 1H), 6.02 (t, 1H), 2.87 (t, 2H), 1.87 (m, 1H), 0.95 (d, 6H) ppm; ES-MS *m/z* 387 (MH<sup>+</sup>).

15

**Example 35**

**Isonicotinaldehyde [1-(3-ethoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone**



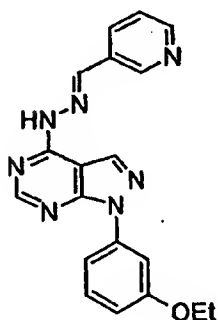
5

1-(3-Ethoxyphenyl)-4-hydrazino-1*H*-pyrazolo[3,4-*d*]pyrimidine (Intermediates

Example 1) (0.050 g, 0.185 mmol) was treated with Isonicotinaldehyde (0.059 g, 0.55  
10 mmol) as described for nicotinaldehyde [1-(3-methylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone (Example 1) to give 0.051 g (77%) of product as a white solid.

<sup>1</sup>H NMR (DMSO) δ 12.50 (br s, 1H), 8.75 (m, 3H), 8.58 (s, 1H), 8.30 (s, 1H), 7.85 (m, 4H),

15 7.49 (t, 1H), 6.96 (d, 1H), 4.14 (q, 2H), 1.40 (t, 3H) ppm; ES-MS *m/z* 360 (MH<sup>+</sup>).

**Example 36****Nicotinaldehyde [1-(3-ethoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone**

5

1-(3-Ethoxyphenyl)-4-hydrazino-1H-pyrazolo[3,4-d]pyrimidine (Intermediates

Example 1) (0.050 g, 0.185 mmol) was treated with nicotinaldehyde (0.059 g, 0.55

mmol) as described for nicotinaldehyde [1-(3-methylphenyl)-1H-pyrazolo[3,4-

d]pyrimidin-4-yl]hydrazone (Example 1) to give 0.057 g (86%) of product as a white

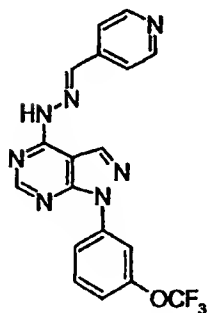
10 solid.

<sup>1</sup>H NMR (DMSO) δ 12.45 (br s, 1H), 8.95 (s, 1H), 8.70 (s, 1H), 8.66 (d, 1H), 8.55 (s, 1H), 8.36 (m, 2H), 7.86 (m, 2H), 7.56 (dd, 1H), 7.49 (t, 1H), 6.96 (d, 1H), 4.14 (q, 2H), 1.40 (t, 3H) ppm; ES-MS m/z 360 (MH<sup>+</sup>).

15

**Example 37**

**Isonicotinaldehyde { 1-[3-(trifluoromethoxy)phenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl} hydrazone**



4-Hydrazino-1-[3-(trifluoromethoxy)phenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidine (Intermediates Example M) (0.050 g, 0.161 mmol) was treated with isonicotinaldehyde (0.051 g, 0.48 mmol) as described for nicotinaldehyde [1-(3-methylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone (Example 1) to give 0.047 g (73%) of product as a pale yellow solid.

10

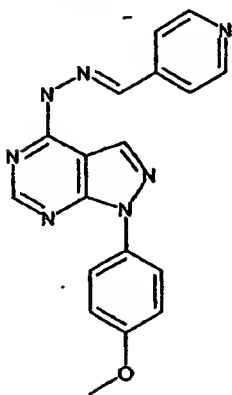
<sup>1</sup>H NMR (DMSO) δ 12.60 (br s, 1H), 8.77 (s, 1H), 8.71 (d, 2H), 8.63 (s, 1H), 8.39 (m, 2H), 8.32 (s, 1H), 7.83 (d, 2H), 7.76 (t, 1H), 7.41 (d, 1H) ppm; ES-MS *m/z* 400 (MH<sup>+</sup>).

15

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**Example 38**

**Isonicotinaldehyde [1-(4-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone**



5

Prepared from 4-Hydrazino-1-(4-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (Intermediates Example N) and isonicotinaldehyde using the general procedure for nicotinaldehyde [1-(3-methylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone

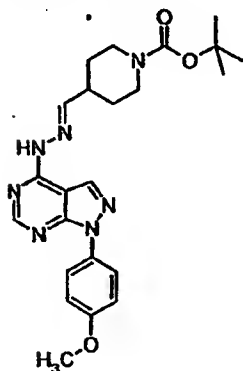
10 (Example 1).

<sup>1</sup>H NMR (300 MHz, DMSO) δ 12.49 (s, 1H), 8.67 (d, 2H), 8.63 (s, 1H), 8.49 (s, 1H), 8.27 (s, 1H), 8.03 (d, 2H), 7.79 (d, 2H), 7.12 (d, 2H), 3.81 (s, 3H) ppm.

15

**Example 39**

**tert-Butyl 4-((E)-{[1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazono} methyl)piperidine-1-carboxylate**



5

Prepared from 4-Hydrazino-1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine (Intermediates Example N) and tert-butyl 4-formylpiperidine-1-carboxylate using the general procedure for nicotinaldehyde [1-(3-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone (Example 1).

10

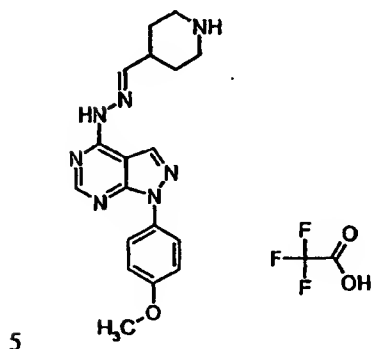
<sup>1</sup>H NMR (300 MHz, DMSO) δ 11.84 (s, 1H), 8.38 (s, 2H), 8.03 (d, 2H), 7.58 (d, 1H), 7.12 (d, 2H), 4.05-3.93 (m, 2H), 3.81 (s, 3H), 2.96-2.76 (m, 2H), 2.63-2.53 (m, 1H), 1.99-1.84 (m, 2H), 1.46-1.36 (m, 11H) ppm.

15



**Example 40**

Piperidine-4-carbaldehyde [1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone trifluoroacetate

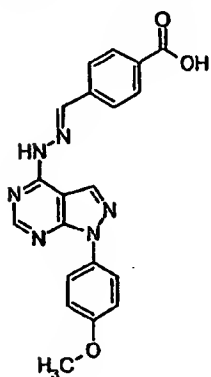


A solution of *tert*-butyl 4-((*E*-{[1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone}methyl)piperidine-1-carboxylate (Example 39) (37 mg, 0.140 mmol),  
10 dichloromethane (10 mL), and TFA (0.5 mL) was stirred at rt for 3h. The resulting mixture was concentrated, washed with dichloromethane, and collected by filtration to give product as a white solid (23 mg, 35% yield).

<sup>1</sup>H NMR (300 MHz, DMSO) δ 12.10–11.78 (s br, 1H), 8.40 (d, 2H), 8.03 (d, 2H), 7.62 (s, 1H), 7.12 (d, 2H), 3.81 (s, 3H), 3.46–3.30 (m, 2H), 3.06–2.90 (m, 2H), 2.80–2.66 (m, 1H), 2.16–2.02 (m, 2H), 1.77–1.61 (m, 2H) ppm; ES-MS *m/z* 352 (MH<sup>+</sup>).  
15

**Example 41**

**4-((E)-{[1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazono}methyl)benzoic acid**



5

Prepared from 4-Hydrazino-1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine (Intermediates Example N) and 4-formylbenzoic acid using the general procedure for nicotinaldehyde [1-(3-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone (Example 1).

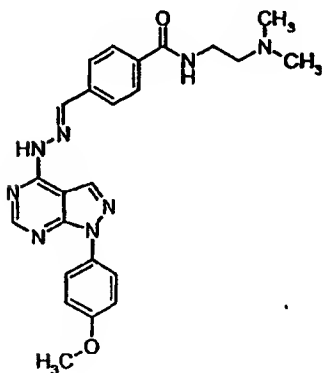
10

<sup>1</sup>H NMR (300 MHz, DMSO) δ 12.60-12.19 (s br, 1H), 8.64 (s, 1H), 8.49 (s, 1H), 8.36 (s, 1H), 8.12-8.01 (m, 4H), 7.97-7.90 (m, 2H), 7.14 (d, 2H), 3.82 (s, 3H) ppm.

15

**Example 42**

*N*-[2-(Dimethylamino)ethyl]-4-((*E*)-{[1-(4-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazono}methyl)benzamide



5

To a solution of 4-((*E*)-{[1-(4-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazono}methyl)benzoic acid (Example 41) (47 mg, 0.120 mmol) in DMF (4 ml),  
 10 was added *N,N*-dimethylethane-1,2-diamine (0.02 ml, 0.180 mmol),  
 diethylcyanophosphonate (0.036 ml, 0.240 mmol), and triethylamine (0.05 ml, 0.360 mmol). The solution was stirred at rt for 1 h, then water and diethyl ether were added. The resulting precipitate was collected by filtration to give pure product (22 mg, yield 40%).

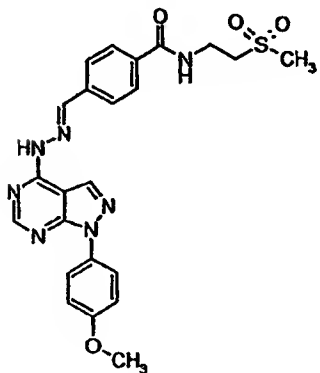
15

<sup>1</sup>H NMR (300 MHz, DMSO) δ 12.32 (s, 1H), 8.63 (s, 1H), 8.53 (t, 1H), 8.48 (s, 1H), 8.34 (s, 1H), 8.10-7.99 (m, 2H), 7.97-7.89 (m, 4H), 7.13 (d, 2H), 3.82 (s, 3H), 3.46-3.32 (m, 2H), 2.55-2.50 (m, 2H), 2.25 (s, 6H) ppm; ES-MS *m/z* 459 (MH<sup>+</sup>).

20

**Example 43**

**4-((*E*)-{[1-(4-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazono}methyl)-*N*-[2-(methylsulfonyl)ethyl]benzamide**



5

To a solution of 4-((*E*)-{[1-(4-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazono}methyl)benzoic acid (Example 41) (47 mg, 0.12 mmol) in DMF (4 ml),  
 10 was added 2-(methylsulfonyl)ethanamine hydrochloride (29 mg, 0.180 mmol), diethylcyanophosphonate (0.036 ml, 0.240 mmol), and triethylamine (0.05 ml, 0.360 mmol). The solution was stirred at rt for 16 h, then water and diethyl ether were added. The resulting precipitate was collected by filtration to give pure product (45 mg, yield 76%).

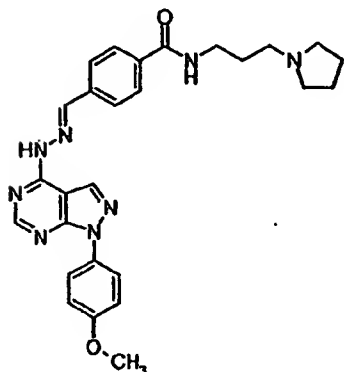
15

<sup>1</sup>H NMR (400 MHz, DMSO) δ 12.33 (s, 1H), 8.81 (t, 1H), 8.63 (s, 1H), 8.46 (s, 1H), 8.33 (s, 1H), 8.04 (d, 2H), 7.99–7.92 (m, 4H), 7.92 (d, 2H), 3.80 (s, 3H), 3.70–3.64 (m, 2H), 3.40–3.35 (m, 2H), 3.30 (s, 3H) ppm; ES-MS *m/z* 494 (MH<sup>+</sup>).

**Example 44**

**4-((*E*)-{[1-(4-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazono}methyl)-*N*-(3-pyrrolidin-1-ylpropyl)benzamide**

5



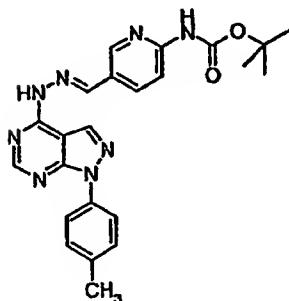
To a solution of 4-((*E*)-{[1-(4-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazono}methyl)benzoic acid (Example 41) (47 mg, 0.12 mmol) in DMF (4 ml),  
 10 was added 3-pyrrolidin-1-ylpropan-1-amine (29 mg, 0.180 mmol),  
 diethylcyanophosphonate (0.036 ml, 0.240 mmol), and triethylamine (0.05 ml, 0.360 mmol). The solution was stirred at rt for 3 h, then water and diethyl ether were added. The resulting precipitate was collected by filtration to give pure product (18 mg, yield  
 15 21%).

<sup>1</sup>H NMR (300 MHz, DMSO) δ 12.33 (s, 1H), 8.66-8.60 (m, 2H), 8.48 (s, 1H), 8.34 (s, 1H), 8.06 (d, 2H), 7.99-7.88 (m, 4H), 7.13 (d, 2H), 3.82 (s, 3H), 3.35-3.28 (m, 2H), 2.55-2.25 (m, 6H), 1.75-1.63 (m, 6H) ppm; ES-MS *m/z* 499 (MH<sup>+</sup>).

20

Example 45

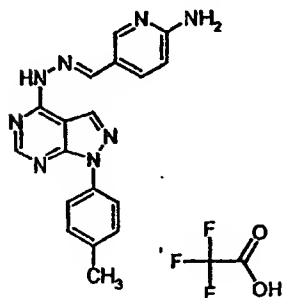
tert-Butyl 5-((E)-{[1-(4-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazono}methyl)pyridin-2-ylcarbamate



5

Prepared from 4-hydrazino-1-(4-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidine  
 10 (Intermediates Example O) and tert-butyl 5-formylpyridin-2-ylcarbamate using the  
 general procedure for nicotinaldehyde [1-(3-methylphenyl)-1H-pyrazolo[3,4-  
 d]pyrimidin-4-yl]hydrazone (Example 1).

<sup>1</sup>H NMR (300 MHz, DMSO) δ 12.26 (s, 1H), 10.08 (s, 1H), 8.64 (s, 1H), 8.57(d, 1H), 8.47  
 15 (s, 1H), 8.32-8.28 (m, 2H), 8.08 (d, 2H), 7.95 (d, 1H), 7.37 (d, 2H), 2.37 (s, 3H), 1.48 (s,  
 9H) ppm; ES-MS m/z 445 (MH<sup>+</sup>).

**Example 46****6-Aminonicotinaldehyde [1-(4-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone**

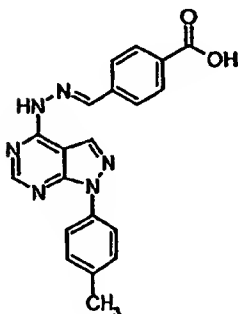
5

A solution of *tert*-butyl 5-((*E*)-{[1-(4-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone}methyl)pyridin-2-yl carbamate (Example 45) (76 mg, 0.171 mg),  
10 dichloromethane (5 ml), and TFA (1 ml) was stirred at RT for 2 h. The mixture was concentrated, dichloromethane was added and the solution was filtered. The filtrate was concentrated to give product as a solid (32 mg, 54% yield).

<sup>1</sup>H NMR (400 MHz, DMSO) δ 12.31 (s, 1H), 8.64 (s, 1H), 8.46–8.43 (m, 2H), 8.72 (s, 1H),  
15 8.18 (s, 1H), 8.17 (d, 3H), 7.36 (d, 2H), 7.01 (d, 1H), 2.36 (s, 3H) ppm; ES-MS *m/z* 336 (MH<sup>+</sup>).

**Example 47**

**4-((*E*)-{[1-(4-methylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazono}methyl)benzoic acid**



5

Prepared from 4-hydrazino-1-(4-methylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (Intermediates Example O) and 4-formylbenzoic acid using the general procedure for nicotinaldehyde [1-(3-methylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone (Example 1).

10

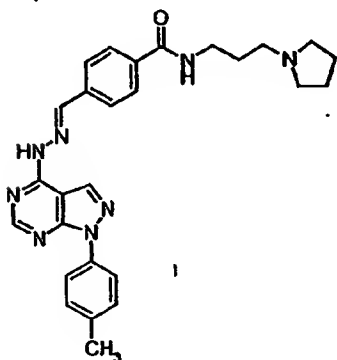
<sup>1</sup>H NMR (300 MHz, DMSO) δ 12.36 (s, 1H), 8.66 (s, 1H), 8.51 (s, 1H), 8.36 (s, 1H), 8.10-8.03 (m, 4H), 7.95 (d, 2H), 7.38 (d, 2H), 2.38 (s, 3H) ppm; AP-MS *m/z* 373 (MH<sup>+</sup>).

15



Example 48

4-((E)-{[1-(4-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazono}methyl)-N-(3-pyrrolidin-1-ylpropyl)benzamide



5

To a solution of 4-((E)-{[1-(4-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazono}methyl)benzoic acid (Example 47) (45 mg, 0.12 mmol) in DMF (4 mL),  
 10 was added 3-pyrrolidin-1-ylpropan-1-amine (29 mg, 0.180 mmol),  
 diethylcyanophosphonate (0.036 mL, 0.240 mmol), and triethylamine (0.05 mL, 0.360 mmol). The solution was stirred at rt for 3 h, then water and diethyl ether were added.  
 The resulting precipitate was collected by filtration to give pure product (18 mg, yield  
 15 31%).

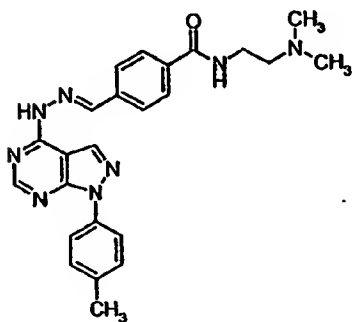
<sup>1</sup>H NMR (300 MHz, DMSO) δ 12.32 (s, 1H), 8.65 (s, 2H), 8.50 (s, 1H), 8.34 (s, 1H), 8.09 (d, 2H), 7.99-7.88 (m, 4H), 7.38 (d, 2H), 3.40-3.28 (m, 2H), 2.55-2.39 (m, 6H), 2.37 (s, 3H), 1.75-1.63 (m, 6H) ppm; ES-MS m/z 483 (MH<sup>+</sup>).

20

**Example 49**

*N*-[2-(Dimethylamino)ethyl]-4-((*E*)-{[1-(4-methylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazono}methyl)benzamide

5



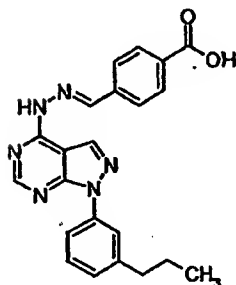
To a solution of 4-((*E*)-{[1-(4-methylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazono}methyl)benzoic acid (Example 47) (45 mg, 0.120 mmol) in DMF (4 mL),  
 10 was added *N,N*-dimethylethane-1,2-diamine (0.02 mL, 0.180 mmol),  
 diethylcyanophosphonate (0.036 mL, 0.240 mmol), and triethylamine (0.05 mL, 0.360 mmol). The solution was stirred at rt for 1 h, then water and diethyl ether were added. The resulting precipitate was collected by filtration to give pure product (21  
 15 mg, yield 40 %).

<sup>1</sup>H NMR (300 MHz, DMSO) δ 12.34 (s, 1H), 8.66 (s, 1H), 8.51 (s, 1H), 8.35 (s, 1H), 8.10 (d, 2H), 7.96-7.89 (m, 4H), 7.39 (d, 2H), 3.48-3.34 (m, 2H), 2.49-2.40 (m, 2H), 2.38 (s, 3H), 2.23 (s, 6H) ppm; ES-MS *m/z* 443 (MH<sup>+</sup>).

20

**Example 50**

**4-((E)-{[1-(3-Propylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]}hydrazono)methyl)benzoic acid**



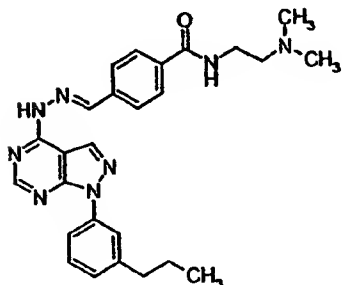
5

Prepared from 4-hydrazino-1-(3-propylphenyl)-1H-pyrazolo[3,4-d]pyrimidine (Intermediates Example P) and 4-formylbenzoic acid using the general procedure for  
 10 nicotinaldehyde [1-(3-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone (Example 1).

<sup>1</sup>H NMR (400 MHz, DMSO) δ 12.44 (s, 1H), 8.68 (s, 1H), 8.53 (s, 1H), 8.37 (s, 1H), 8.09-  
 8.02 (m, 4H), 7.99-7.93 (m, 2H), 7.48 (t, 1H), 7.22 (d, 1H), 2.68 (t, 2H), 1.72-1.61 (m,  
 15 2H), 0.94 (t, 3H) ppm; AP-MS m/z 401 (MH<sup>+</sup>).

**Example 51**

*N*-[2-(Dimethylamino)ethyl]-4-((*E*)-{[1-(3-propylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazono}methyl)benzamide



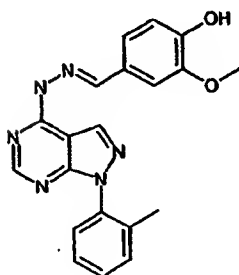
5

To a solution of 4-((*E*)-{[1-(3-propylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazono}methyl)benzoic acid (Example 50) (43 mg, 0.120 mmol) in DMF (4 mL),  
 10 was added *N,N*-dimethylethane-1,2-diamine (0.02 mL, 0.180 mmol),  
 diethylcyanophosphonate (0.036 mL, 0.240 mmol), and triethylamine (0.05 mL, 0.360 mmol). The solution was stirred at RT for 1 h, then water and diethyl ether were added. The resulting precipitate was collected by filtration to give pure product (20  
 15 mg, yield 24%).

<sup>1</sup>H NMR (300 MHz, DMSO) δ 12.33 (s, 1H), 8.67 (s, 1H), 8.52 (s, 1H), 8.35 (s, 1H), 8.06-8.03 (m, 2H), 7.96-7.87 (m, 4H), 7.47 (t, 1H), 7.21 (d, 1H), 3.45-3.34 (m, 2H), 2.72-2.62 (m, 2H), 2.50-2.44 (m, 2H), 2.23 (s, 3H), 1.65 (m, 2H), 0.94 (t, 3H) ppm; ES-MS *m/z* 471  
 20 (MH<sup>+</sup>).

**Example 52****4-Hydroxy-3-methoxybenzaldehyde [1-(2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone**

5



10 Prepared from 4-Hydrazino-1-(2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidine (Intermediates Example Q) and 4-Hydroxy-3-methoxybenzaldehyde using the general procedure for nicotinaldehyde [1-(3-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone (Example 1).

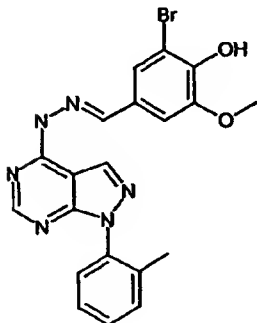
15 <sup>1</sup>H NMR (400 MHz, DMSO) δ 12.10 (s, 1H), 9.58 (s, 1H), 8.55 (s, 1H), 8.28 (s, 1H), 8.18 (s, 1H), 7.33-7.44 (m, 5H), 7.21 (b, 1H), 6.87 (d, 1H), 3.86 (s, 3H), 2.05 (s, 3H) ppm. ES-MS m/z 375 (MH<sup>+</sup>).

20

141

Example 53

3-Bromo-4-hydroxy-5-methoxybenzaldehyde [1-(2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone

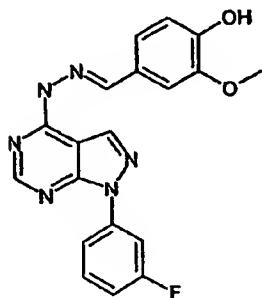


5

Prepared from 4-hydrazino-1-(2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidine  
10 (Intermediates Example Q) and 3-Bromo-4-hydroxy-5-methoxybenzaldehyde using  
the general procedure for nicotinaldehyde [1-(3-methylphenyl)-1H-pyrazolo[3,4-  
d]pyrimidin-4-yl]hydrazone (Example 1).

<sup>1</sup>H NMR (400 MHz, DMSO) δ 12.15 (s, 1H), 10.03 (s, 1H), 8.52 (s, 1H), 8.30 (s, 1H), 8.16  
15 (s, 1H), 7.37-7.46 (m, 6H), 3.93 (s, 3H), 2.05 (s, 3H). ES-MS m/z 454 (MH<sup>+</sup>).

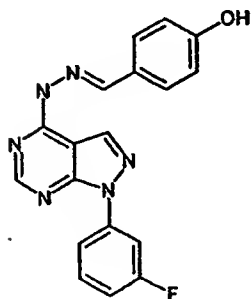
20

Example 544-Hydroxy-3-methoxybenzaldehyde [1-(3-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone

- Prepared from 1-(3-fluorophenyl)-4-hydrazino-1H-pyrazolo[3,4-d]pyrimidine (Intermediates Example R) and 4-hydroxy-3-methoxybenzaldehyde using the general procedure for nicotinaldehyde [1-(3-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone (Example 1).
- 10

<sup>1</sup>H NMR (400 MHz, DMSO) δ 12.14 (s, 1H), 9.59 (s, 1H), 8.58 (s, 1H), 8.45 (s, 1H), 8.12-8.17 (m, 3H), 7.58 (d, 1H), 7.32 (s, 1H), 7.19 (m, 2H), 6.86 (d, 1H), 3.86 (s, 3H) ppm. ES-MS m/z 379 (MH<sup>+</sup>).

15

Example 554-Hydroxybenzaldehyde [1-(3-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone

5

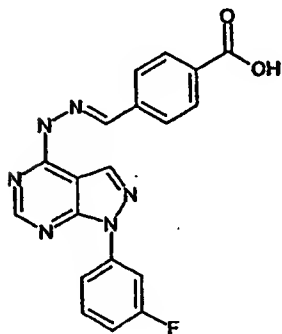
- Prepared from 1-(3-fluorophenyl)-4-hydrazino-1H-pyrazolo[3,4-d]pyrimidine  
10 (Intermediates Example R) and 4-hydroxybenzaldehyde using the general procedure  
for nicotinaldehyde [1-(3-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone  
(Example 1).

- <sup>1</sup>H NMR (400 MHz, DMSO) δ 12.09 (s, 1H), 9.95 (s, 1H), 8.60 (s, 1H), 8.44 (s, 1H), 8.12-  
15 8.17 (m, 3H), 7.55-7.64 (m, 3H), 7.16 (t, 1H), 6.86 (d, 2H). ES-MS m/z 349 (MH<sup>+</sup>).



**Example 56**

**4-((*E*)-{[1-(3-fluorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazono}methyl)benzoic acid**

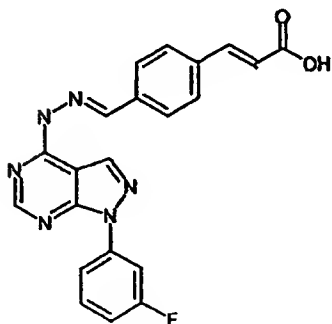


5

- Prepared from 1-(3-fluorophenyl)-4-hydrazino-1*H*-pyrazolo[3,4-*d*]pyrimidine (Intermediates Example R) and 4-formylbenzoic using the general procedure for nicotinaldehyde [1-(3-methylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone (Example 1).

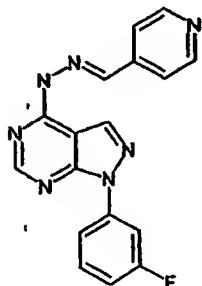
- <sup>1</sup>H NMR (400 MHz, DMSO)  $\delta$  11.85 (s, 1H), 8.64 (s, 1H), 8.50 (s, 1H), 8.40 (s, 1H), 8.12 (m, 2H), 8.00 (d, 2H), 7.85 (d, 2H), 7.58 (m, 1H), 7.17 (t, 1H) ppm. ES-MS *m/z* 377 (MH<sup>+</sup>).

15

**Example 57****4-Vinylbenzaldehyde [1-(3-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone**

Prepared from 1-(3-fluorophenyl)-4-hydrazino-1H-pyrazolo[3,4-d]pyrimidine  
(Intermediates Example R) and 4-vinylbenzaldehyde using the general procedure for  
10 nicotinaldehyde [1-(3-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone  
(Example 1).

<sup>1</sup>H NMR (400 MHz, DMSO) δ 8.62 (s, 1H), 8.49 (s, 1H), 8.27 (s, 1H), 8.12 (m, 2H), 7.80 (d,  
2H), 7.73 (d, 2H), 7.58 (m, 1H), 7.51 (d, 1H), 7.16 (m, 1H), 6.56 (d, 1H) ppm. ES-MS m/z  
15 403 (MH<sup>+</sup>).

**Example 58****Isonicotinaldehyde [1-(3-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone**

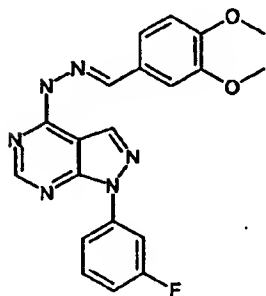
5

Prepared from 1-(3-fluorophenyl)-4-hydrazino-1H-pyrazolo[3,4-d]pyrimidine  
10 (Intermediates Example R) and isonicotinaldehyde using the general procedure for  
nicotinaldehyde [1-(3-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone  
(Example 1).

<sup>1</sup>H NMR (400 MHz, DMSO) δ 12.45 (s, 1H), 8.64 (s, 3H), 8.52 (s, 1H), 8.22 (s, 1H), 8.10  
15 (m, 2H), 7.73 (d, 2H), 7.58 (m, 1H), 7.17 (t, 1H) ppm. ES-MS m/z 334 (MH<sup>+</sup>).

**Example 59**

**3,4-Dimethoxybenzaldehyde [1-(3-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone**



5

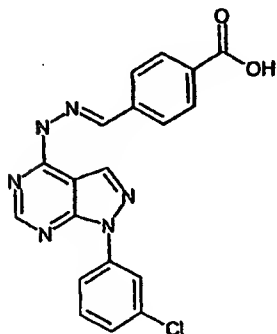
Prepared from 1-(3-fluorophenyl)-4-hydrazino-1H-pyrazolo[3,4-d]pyrimidine (Intermediates Example R) and 3,4-dimethoxybenzaldehyde using the general procedure for nicotinaldehyde [1-(3-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone (Example 1).

<sup>1</sup>H NMR (300 MHz, DMSO) δ 12.24 (s, 1H), 8.61 (s, 1H), 8.50 (s, 1H), 8.23 (s, 1H), 8.17 (m, 2H), 7.62 (m, 1H), 7.39 (s, 1H), 7.32 (d, 1H), 7.21 (t, 1H), 7.08 (d, 1H), 3.90 (s, 3H), 3.84 (s, 3H) ppm. ES-MS m/z 393 (MH<sup>+</sup>).

15

**Example 60**

4-((E)-{1-(3-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl}hydrazono)methylbenzoic acid



5

Prepared from 1-(3-chlorophenyl)-4-hydrazino-1H-pyrazolo[3,4-d]pyrimidine (Intermediates Example S) and 4-formylbenzoic using the general procedure for nicotinaldehyde [1-(3-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone (Example 1).

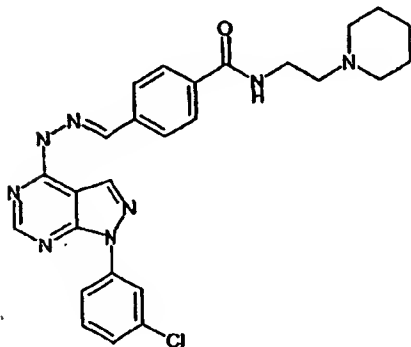
10

<sup>1</sup>H NMR (400 MHz, DMSO) δ 12.34 (s, 1H), 8.64 (s, 1H), 8.52 (s, 1H), 8.38 (s, 1H), 8.32 (s, 1H), 8.20 (d, 1H), 8.00 (d, 2H), 7.89 (d, 2H), 7.57 (t, 1H), 7.39 (d, 1H) ppm.

15

**Example 61**

**4-((*E*)-{[1-(3-chlorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazono}methyl)-*N*-(2-piperidin-1-ylethyl)benzamide**



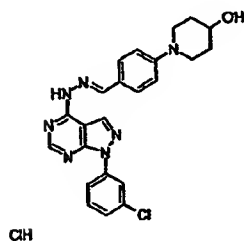
5

Prepared from 4-((*E*)-{[1-(3-chlorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazono}methyl)benzoic acid (Example 60) and 2-piperidin-1-ylethanamine using the method described for *N*-[2-(dimethylamino)ethyl]-4-((*E*)-{[1-(3-propylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazono}methyl)benzamide (Example 51).

<sup>1</sup>H NMR (400 MHz, DMSO) δ 12.39 (s, 1H), 8.67 (s, 1H), 8.52 (s, 1H), 8.46 (m, 1H), 8.39 (m, 1H), 8.32 (s, 1H), 8.22 (d, 1H), 7.82-7.92 (m, 4H), 7.58 (t, 1H), 7.40 (d, 1H), 3.36 (m, 2H), 2.36-2.46 (m, 6H), 1.47 (m, 4H), 1.35 (m, 2H) ppm. ES-MS *m/z* 504 (MH<sup>+</sup>).

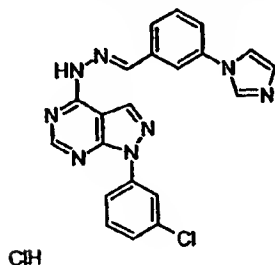
Example 624-(4-Hydroxy-piperidin-1-yl)-benzaldehyde [1-(3-chloro-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone hydrochloride

5



To a solution of 4-hydrazino-1-(3-chloro-phenyl)-1H-pyrazolo[3,4-d]pyrimidine  
 10 (Intermediates Example S) (50 mg, 0.17mmol) in EtOH (3 mL) was added 4-(4-  
 hydroxy-piperidin-1-yl)-benzaldehyde (62 mg, 0.25 mmol) . The reaction mixture was  
 refluxed overnight. The cooled solution was filtered to collect precipitate, which was  
 dissolved in HCl -MeOH and evaporated in vacuo to give a solid. (32.3mg, 39% yield )

15 <sup>1</sup>H NMR (400 MHz, DMSO) δ8.66 (s, 1H), 8.51 (s, 1H), 8.42 (s, 1H), 8.25-8.24 (m, 2H),  
 7.74 (d, 2H), 7.62 (t, 1H), 7.44 (d, 1H), 7.25 (d, 2H), 3.68 (m, 5H), 3.13 (m, 4H) ppm; ES-  
 MS m/z 448 (MH<sup>+</sup>).

**Example 63****3-Imidazol-1-yl-benzaldehyde [1-(3-chloro-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone hydrochloride**

5

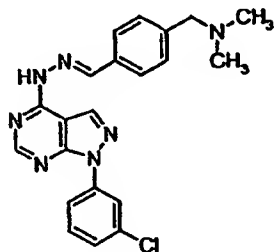
To a solution of 4-hydrazino-1-(3-chloro-phenyl)-1H-pyrazolo[3,4-d]pyrimidine (Intermediates Example S) (50 mg, 0.17mmol) in EtOH (3 mL) was added 3-imidazol-1-yl-benzaldehyde (52 mg, 0.25 mmol). The reaction mixture was refluxed overnight.

- 10 The cooled solution was filtered to collect precipitate, which was dissolved in HCl - MeOH and evaporated in vacuo to give a solid (82.7mg, 99% yield).

<sup>1</sup>H NMR (400 MHz, DMSO) δ 9.86 (brs, 1H), 8.59 (s, 1H), 8.43 (br, 2H), 8.23-8.26 (m, 2H), 8.06 (d, 1H), 7.99 (s, 1H), 7.88 (d, 1H), 7.78 (t, 1H), 7.63 (t, 1H), 7.45 (d, 1H) ppm;

- 15 ES-MS m/z 415 (MH<sup>+</sup>).

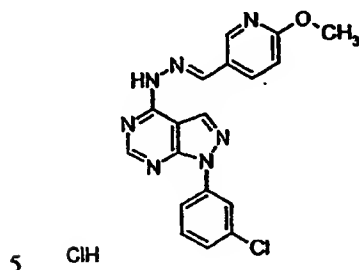


**Example 64****4-Dimethylaminomethyl-benzaldehyde [1-(3-chloro-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone**

5 ClH

To a solution of 4-hydrazino-1-(3-chloro-phenyl)-1H-pyrazolo[3,4-d]pyrimidine (Intermediates Example S) (50 mg, 0.17mmol) in EtOH (3 mL) was added 4-dimethylaminomethyl-benzaldehyde (50 mg, 0.25 mmol). The reaction mixture was refluxed overnight. The cooled solution was filtered to collect pure product (23.0mg, 33% yield).

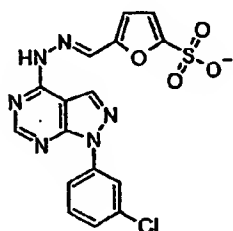
<sup>1</sup>H NMR (400 MHz, DMSO) δ12.25 (brs, 1H), 8.67 (s, 1H), 8.53 (s, 1H), 8.43 (s, 1H), 8.31 (s, 1H), 8.24(d, 1H), 7.78 (d, 2H), 7.61 (t, 1H), 7.41-7.43 (m 3H) 3.44 (s, 2H), 2.17 (s, 6H) ppm; ES-MS m/z 406 (MH<sup>+</sup>).

Example 656-Methoxy-pyridine-3-carbaldehyde[1-(3-chloro-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone

- To a solution of 4-hydrazino-1-(3-chloro-phenyl)-1H-pyrazolo[3,4-d]pyrimidine (Intermediates Example S) (50 mg, 0.17mmol) in EtOH (3 mL) was added 6-methoxy-pyridine-3-carbaldehyde (42 mg, 0.25 mmol). The reaction mixture was refluxed overnight. The cooled solution was filtered to collect pure product (56.8 mg, 88% yield)
- 15     <sup>1</sup>H NMR (400 MHz, DMSO) δ12.34 (brs, 1H), 8.68 (s, 1H), 8.52 (s, 1H), 8.49 (s, 1H), 8.42 (s, 1H), 8.30-8.34 (m, 2H), 8.27 (d, 1H), 8.62 (t, 1H), 7.45 (d, 1H), 6.97 (d, 1H), 3.93 (s, 3H) ppm; ES-MS m/z 380 (MH<sup>+</sup>).

**Example 66****5-Formyl-furan-2-sulfonic acid [1-(3-chloro-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone**

5

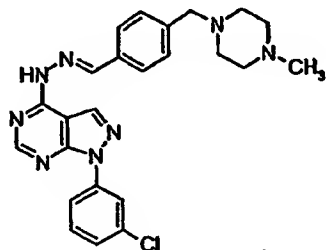
Na<sup>+</sup>

To a solution of 4-hydrazino-1-(3-chloro-phenyl)-1H-pyrazolo[3,4-d]pyrimidine (Intermediates Example S) (50 mg, 0.17mmol) in EtOH (3 mL) was added 5-formyl-furan-2-sulfonic acid sodium salt (60mg, 0.25 mmol). The reaction mixture was refluxed overnight. The cooled solution was filtered to collect pure product (69 mg, 92% yield)

<sup>1</sup>H NMR (400 MHz, DMSO) δ 12.32 (brs, 1H), 8.65 (s, 1H), 8.54 (s, 1H), 8.46 (s, 1H), 8.28 (d, 1H), 8.16 (s, 1H), 7.61 (t, 1H), 7.43 (d, 1H), 6.99 (d, 1H), 6.57 (d, 1H) ppm; ES-MS m/z 419 (MH<sup>+</sup>).

**Example 67**

**4-(4-Methyl-piperazin-1-ylmethyl)-benzaldehyde(1-(3-chloro-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)hydrazone dihydrochloride**



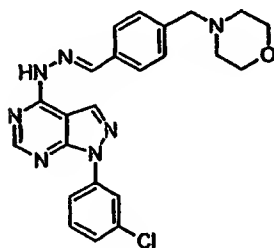
5 ClH

To a solution of 4-hydrazino-1-(3-chloro-phenyl)-1H-pyrazolo[3,4-d]pyrimidine  
 10 (Intermediates Example S) (39 mg, 0.13 mmol) in EtOH (5 mL) were added 2N HCl  
 (0.5mL) and 1-(4-diethoxymethyl-benzyl)-4-methyl-piperazine (42 mg, 0.14 mmol).  
 The reaction mixture was refluxed overnight. The cooled solution was filtered to  
 collect pure product (66 mg, 95% yield).

15 <sup>1</sup>H NMR (400 MHz, DMSO) δ12.42 (brs, 1H), 8.71 (s, 1H), 8.57 (s, 1H), 8.43 (s, 1H), 8.36  
 (s, 1H), 8.25 (d, 1H), 7.88-7.94 (m, 2H), 7.60-7.70 (m, 2H), 7.63 (t, 1H), 7.45 (d, 1H), 3.1-  
 3.6 (br, 10H), 2.81 (s, 3H) ppm; ES-MS m/z 461 (MH<sup>+</sup>).

**Example 68**

**4-Morpholin-4-ylmethyl-benzaldehyde[1-(3-chloro-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone, hydrochloride**



5

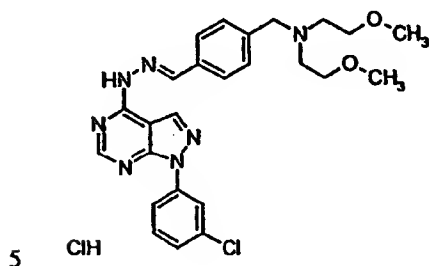
ClH

To a solution of 4-hydrazino-1-(3-chloro-phenyl)-1H-pyrazolo[3,4-d]pyrimidine (Intermediates Example S) (38 mg, 0.13 mmol) in EtOH (5 mL) were added 2N HCl (0.5mL) and 4-(4-diethoxymethyl-benzyl)-morpholine (39 mg, 0.14 mmol). The reaction mixture was refluxed overnight. The cooled solution was filtered to collect pure product (45 mg, 71% yield).

<sup>1</sup>H NMR (400 MHz, DMSO) δ 12.45 (brs, 1H), 10.60 (brs, 1H), 8.73 (s, 1H), 8.57 (s, 1H), 8.42 (s, 1H), 8.37 (s, 1H), 8.24 (d, 1H), 7.95 (d, 2H), 7.69 (d, 2H), 7.63 (t, 1H), 7.45 (d, 1H), 4.41 (m, 2H), 3.98 (m, 2H), 3.72 (m, 2H), 2.29 (m, 2H), 2.12 (m, 2H) ppm; ES-MS m/z 448 (MH<sup>+</sup>).

**Example 69**

**4-{ [Bis-(2-methoxy-ethyl)-amino]-methyl}-benzaldehyde[1-(3-chloro-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone hydrochloride**

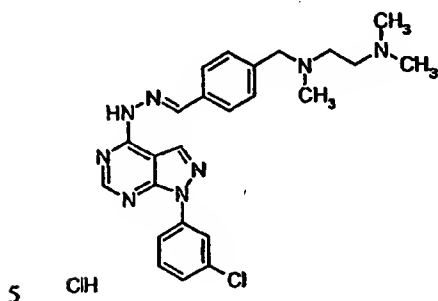


To a solution of 4-hydrazino-1-(3-chloro-phenyl)-1H-pyrazolo[3,4-d]pyrimidine (Intermediates Example S) (32 mg, 0.11 mmol) in EtOH (5 mL) were added 2N HCl (0.5mL) and *N*-[4-(dimethoxymethyl)benzyl]-2-methoxy-*N*-(2-methoxyethyl)ethanamine (43 mg, 0.12 mmol). The reaction mixture was refluxed overnight. The cooled solution was filtered to collect pure product (24 mg, 41% yield).

<sup>1</sup>H NMR (400 MHz, DMSO) δ 12.45 (brs, 1H), 10.03 (brs, 1H), 8.73 (s, 1H), 8.57(s, 1H), 8.43 (s, 1H), 8.37 (s, 1H), 8.24 (d, 1H), 7.95 (d, 2H), 7.71(d, 2H), 7.62 (t, 1H), 7.43 (d, 1H), 4.47 (m, 2H), 3.70 (m, 4H), 3.31(m, 4H), 3.31 (s, 6H) ppm; ES-MS *m/z* 494 (MH<sup>+</sup>)

**Example 70**

**4-[[[(2-Dimethylamino-ethyl)-methyl-amino]-methyl]-benzaldehyde[1-(3-chloro-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone dihydrochloride**



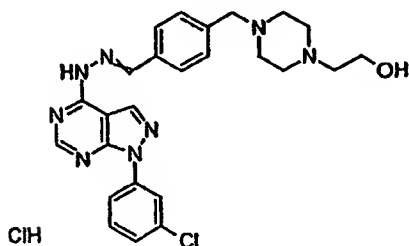
To a solution of 4-hydrazino-1-(3-chloro-phenyl)-1H-pyrazolo[3,4-d]pyrimidine (Intermediates Example S) (35 mg, 0.12 mmol) in EtOH (5 mL) were added 2N HCl (0.5mL) and N-(4-diethoxymethyl-benzyl)-N,N',N'-trimethyl-ethane-1,2-diamine (48 mg, 0.13 mmol). The reaction mixture was refluxed overnight. The cooled solution was filtered to collect pure product (53 mg, 82 %yield).

<sup>1</sup>H NMR (400 MHz, DMSO) δ 12.45 (brs, 1H), 10.86 (brs, 1H), 10.50 (brs, 1H), 8.73 (s, 1H), 8.57 (s, 1H), 8.43 (s, 1H), 8.37 (s, 1H), 8.26 (d, 1H), 7.95 (m, 2H), 7.75 (m, 2H), 7.63 (t, 1H), 7.47 (d, 1H), 4.62 (m, 1H), 4.35 (m, 1H), 3.61(m, 2H), 2.86 (s, 6H), 2.73 (m, 2H) ppm; ES-MS m/z 463 (MH<sup>+</sup>).

**Example 71**

**4-[4-(2-Hydroxy-ethyl)-piperazin-1-ylmethyl]-benzaldehyde[1-(3-chloro-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone dihydrochloride**

5

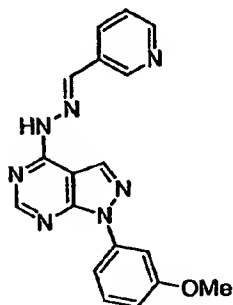


To a solution of 4-hydrazino-1-(3-chloro-phenyl)-1H-pyrazolo[3,4-d]pyrimidine (Intermediates Example S) (34 mg, 0.11 mmol) in EtOH (5 mL) were added 2N HCl (0.5mL) and 2-[4-(4-diethoxymethyl-benzyl)-piperazin-1-yl]-ethanol (55 mg, 0.17 mmol). The reaction mixture was refluxed overnight. The cooled solution was filtered to collect pure product (58 mg, 94 % yield).

<sup>1</sup>H NMR (400 MHz, DMSO) δ 12.40 (brs, 1H), 8.72 (s, 1H), 8.57 (s, 1H), 8.43 (s, 1H), 8.36 (s, 1H), 8.26 (d, 1H), 7.93 (d, 2H), 7.68 (m, 2H), 7.63 (t, 1H), 7.45 (d, 1H), 3.76 (m, 2H), 3.68 (m, 2H), 3.24 (m, 10H) ppm; ES-MS m/z 491, 493 (MH<sup>+</sup>).

20



**Example 72****Nicotinaldehyde [1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone**

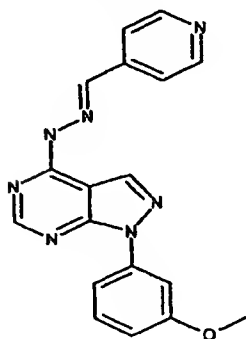
5

Nicotinaldehyde (0.22 mL, 2.34 mmol) was added to a suspension of 4-hydrazino-1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine (Intermediates Example T) (0.200 g, 0.78 mmol) in 10 mL of absolute ethanol. The mixture was heated at reflux for two hours. After cooling to room temperature the solid product was collected by filtration, washed with ethanol, and dried under vacuum to give 0.241 g (91%) of a white solid.

15

<sup>1</sup>H NMR (400 MHz, DMSO) δ 12.45 (br s, 1H), 8.91 (s, 1H), 8.66 (s, 1H), 8.60 (d, 1H), 8.50 (s, 1H), 8.33 (s, 1H), 8.32 (d, 1H), 7.85 (m, 2H), 7.52 (dd, 1H), 7.46 (t, 1H), 6.94 (dd, 1H), 3.83 (s, 3H) ppm. ES-MS m/z 309 (MH<sup>+</sup>).

20

**Example 73****Isonicotinaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone**

5

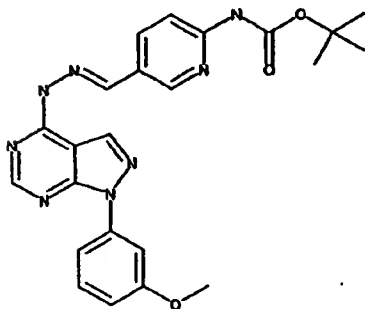
Prepared from 4-hydrazino-1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (Intermediates Example T) and isonicotinaldehyde using the general procedure for  
10 nicotinaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone (Example 72).

<sup>1</sup>H NMR (300 MHz, DMSO) δ 12.51 (s, 1H), 8.68-8.66 (m, 3H), 8.54 (s, 1H), 8.26 (s, 1H), 7.84 (d, 2H), 7.77 (d, 2H), 7.47 (t, 1H), 6.94 (d, 1H), 3.83 (s, 3H).ppm.

15

**Example 74**

*tert*-butyl 5-((*E*)-{[1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazono}methyl)pyridin-2-ylcarbamate



5

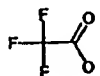
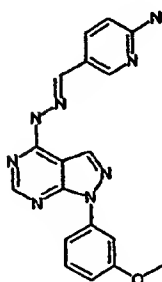
Prepared from 4-hydrazino-1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (Intermediates Example T) and *tert*-butyl 5-formylpyridin-2-ylcarbamate using the general procedure for nicotinaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone (Example 72).

<sup>1</sup>H NMR (300 MHz, DMSO) δ 12.23 (s, 1H), 10.07 (s, 1H), 8.65 (s, 1H), 8.55 (s, 1H), 8.48 (s, 1H), 8.28 (d, 1H), 8.26 (s, 1H), 7.93 (d, 1H), 7.86-7.83 (m, 2H), 7.46 (t, 1H), 6.93 (dd, 1H), 3.83 (s, 3H), 1.48 (s, 9H) ppm.

15

**Example 75****6-Aminonicotinaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone trifluoroacetate**

5



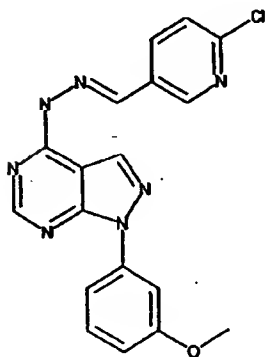
- 10 Trifluoroacetic acid (3 mL) was added to a suspension of *tert*-butyl 5-{(E)-[1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone)methyl}pyridin-2-ylcarbamate (Example 74) (0.070 g; 0.15 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL). The mixture was stirred at RT for 3 days then solvent removed to give the title compound (0.075 g) as a white solid (100%).

15

<sup>1</sup>H NMR (300 MHz, DMSO) δ 8.65-8.48 (m, 4H), 8.29 (s, 1H), 8.18 (s, 1H), 7.83 (m, 2H), 7.45 (m, 1H), 7.10-7.08 (m, 1H), 6.92 (m, 1H), 3.82 (s, 3H) ppm; ES-MS *m/z* 361 (MH<sup>+</sup>).

**Example 76**

**6-chloronicotinaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone**



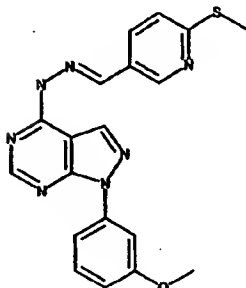
5

- Prepared from 4-hydrazino-1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (Intermediates Example T) and 6-chloronicotinaldehyde using the general procedure for nicotinaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone (Example 72).

- <sup>1</sup>H NMR (300 MHz, DMSO) δ 12.49 (s, 1H), 8.76 (s, 1H), 8.67 (s, 1H), 8.54 (s, 1H), 8.41 (d, 1H), 8.33 (s, 1H), 7.90-7.86 (m, 2H), 7.63 (d, 1H), 7.49 (t, 1H), 6.97 (d, 1H), 3.86 (s, 3H) ppm.

15

165

**Example 77****6-(methylthio)nicotinaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone**

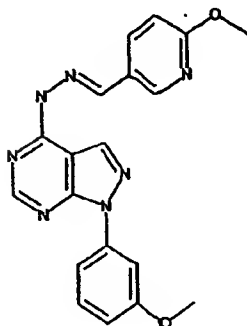
5

A mixture of 6-chloronicotinaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone (Example 76) (0.138 g; 0.36 mmol) and sodium  
thiomethoxide (0.126 g; 1.82 mmol) in DMSO (5 mL) were heated to 105 °C for 1 h.  
The solution was cooled to RT then water (3 mL) and MeOH (3 mL) were added. The  
solid was filtered and dried to give title compound (102 mg) as a off-white powder  
(72%).

15

<sup>1</sup>H NMR (300 MHz, DMSO) δ 12.33 (s, 1H), 8.74 (s, 1H), 8.65 (s, 1H), 8.50 (s, 1H), 8.28 (s,  
1H), 8.20 (d, 1H), 7.88-7.85 (m, 2H), 7.48 (t, 1H), 7.42 (d, 1H), 6.95 (d, 1H), 3.84 (s, 3H),  
2.57 (s, 3H) ppm; ES-MS m/z 390.0 (MH<sup>+</sup>).

20

**Example 78****6-Methoxynicotinaldehyde [1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone**

5

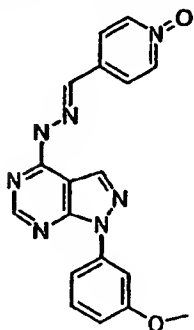
A mixture of 6-chloronicotinaldehyde [1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone (Example 76) (0.11 g; 0.29 mmol) and sodium methoxide (0.11 g; 2.09 mmol) in DMSO (5 mL) were heated to 105 °C for 1h. The solution was cooled to RT then water (25 mL) was added. The solid was filtered, washed with MeOH (3 mL) then Et<sub>2</sub>O (5 mL) and dried to give title compound (68 mg) as a off-white powder (63%).

<sup>1</sup>H NMR (300 MHz, DMSO) δ 12.30 (s, 1H), 8.67 (s, 1H), 8.51 (s, 1H), 8.50 (s, 1H), 8.36-8.31 (m, 2H), 7.90-7.88 (m, 2H), 7.50 (t, 1H), 6.99 (d, 2H), 3.94 (s, 3H), 3.87 (s, 3H) ppm; ES-MS m/z 376.0 (MH<sup>+</sup>).

15

**Example 79**

**Isonicotinaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone 1-oxide**



5

The title compound was prepared according to the general procedure for  
nicotinaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone  
(Example 72) from 4-hydrazino-1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine  
10 (Intermediates Example T) (100 mg, 0.39 mmol) and isonicotinaldehyde 1-oxide (85  
mg, 0.69 mmol) to give the product as a orange solid (127 mg, 90%).

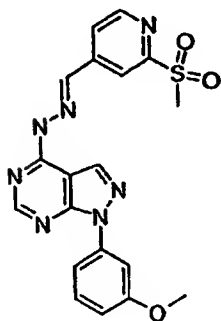
<sup>1</sup>H NMR (DMSO) δ 12.47 (s, 1H), 8.67 (s, 1H), 8.53 (s, 1H), 8.24 (d, 3H), 7.86 (m, 4H),  
7.48 (t, 1H), 6.94 (dd, 1H), 3.84 (s, 3H) ppm; ES-MS *m/z* 362 (MH<sup>+</sup>).

15



**Example 80**

**2-(Methylsulfonyl)isonicotinaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone hydrochloride**



5

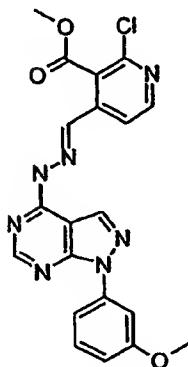
To 4-(diethoxymethyl)-2-(methylsulfonyl)pyridine (Intermediates Example V) (120 mg, 0.46 mmol) in THF (5 mL) was added 4-hydrazino-1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (Intermediates Example T) (90 mg, 0.35 mmol) and 1N aqueous hydrochloric acid (5 mL). The mixture was heated in a 90 C oil bath for ca. 1.75 h. After cooling to RT the resulting solid was collected by filtration and washed with ether to give the HCl salt of the product as a white solid (93 mg, 57%).

<sup>1</sup>H NMR (DMSO) δ 8.86 (d, 1H), 8.64 (s, 1H), 8.58 (s, 1H), 8.42 (brs, 1H), 8.34 (brs, 1H), 8.16 (d, 1H), 7.84 (m, 2H), 7.48 (t, 1H), 6.96 (d, 1H), 5.11 (brs, 2H), 3.84 (s, 3H), 3.34 (s, 3H) ppm. ES-MS m/z 424 (MH<sup>+</sup>).

20

**Example 81**

Methyl 2-chloro-4-((E)-{[1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazono} methyl)nicotinate hydrochloride



5

To methyl 2-chloro-4-(diethoxymethyl)nicotinate (95 mg, 0.35 mmol) in THF (5 mL)  
 10 was added 4-hydrazino-1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine  
 (Intermediates Example T) (80 mg, 0.31 mmol) and 1N aqueous hydrochloric acid (5  
 mL). The mixture was heated in a 90 °C oil bath for ca. 3.5 h. After cooling to RT the  
 resulting solid was collected by filtration and washed with ether to give the HCl salt of  
 the product as a white solid (60 mg, 41%).

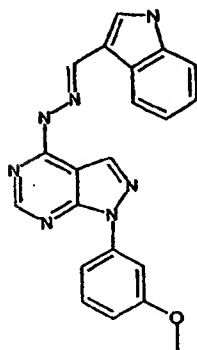
15

<sup>1</sup>H NMR (DMSO) δ 8.66 (s, 1H), 8.59 (m, 2H), 8.30 (s, 1H), 8.12 (d, 1H), 7.85 (m, 2H),  
 7.48 (t, 1H), 6.96 (dd, 1H), 4.91 (brs, 2H), 3.93 (s, 3H), 3.84 (s, 3H) ppm; ES-MS m/z 438  
 (MH<sup>+</sup>).

20

**Example 82**

**1*H*-Indole-3-carbaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone**



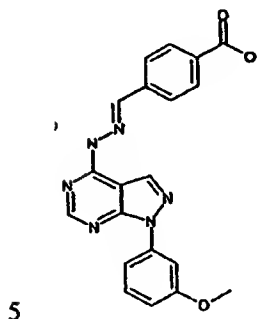
5

Prepared from 4-hydrazino-1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (Intermediates Example T) and 1*H*-indole-3-carbaldehyde using the general  
10 procedure for nicotinaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone (Example 72).

<sup>1</sup>H NMR (300 MHz, DMSO) δ 11.95 (s, 1H), 11.74 (s, 1H), 8.67 (s, 1H), 8.53 (s, 1H), 8.42 (s, 1H), 8.19 (s, 1H), 7.94-7.86 (m, 3H), 7.49-7.43 (m, 2H), 7.27-7.24 (m, 2H), 6.93 (m,  
15 1H), 3.83 (s, 3H) ppm.

**Example 83**

**4-((E)-{[1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazono}methyl)benzoic acid**

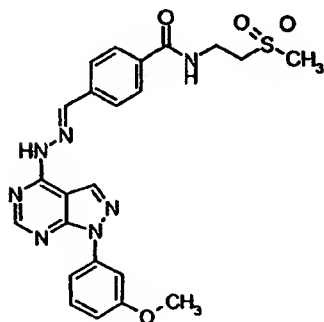


Prepared from 4-hydrazino-1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine  
(Intermediates Example T) and 4-formylbenzoic acid using the general procedure for  
10 nicotinaldehyde [1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone  
(Example 72).

<sup>1</sup>H NMR (300 MHz, DMSO) δ 12.90-12.49 (s br, 2H), 8.67 (s, 1H), 8.51 (s, 1H), 8.34 (s,  
1H), 8.02 (d, 2H), 7.93 (d, 2H), 7.87-7.83 (m, 2H), 7.46 (t, 1H), 6.93 (d, 1H), 3.83 (s, 3H)  
15 ppm.

Example 84

4-((*E*)-{[1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazono} methyl)-*N*-[2-(methylsulfonyl)ethyl]benzamide



5

To a solution of 4-((*E*)-{[1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazono} methyl)benzoic acid (Example 83) (47 mg, 0.12 mmol) in DMF (4 mL),  
 10 was added 2-(methylsulfonyl)ethanamine hydrochloride (29 mg, 0.180 mmol),  
 diethylcyanophosphonate (0.036 mL, 0.240 mmol), and triethylamine (0.05 mL, 0.360 mmol). The solution was stirred at rt for 16 h, then water and diethyl ether were added. The resulting precipitate was collected by filtration to give pure product (48  
 15 mg, yield 81%).

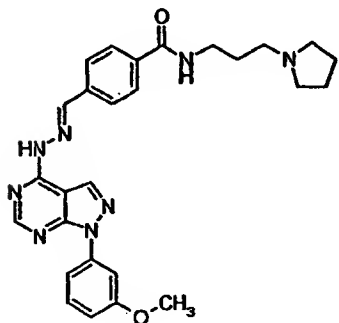
<sup>1</sup>H NMR (300 MHz, DMSO) δ 12.39 (s, 1H), 8.83 (t, 1H), 8.69 (s, 1H), 8.53 (s, 1H), 8.35 (s, 1H), 7.99-7.92 (m, 4H), 7.88-7.85 (m, 2H), 7.48 (t, 1H), 6.95 (dd, 1H), 3.84 (s, 3H), 3.70 (q, 2H), 3.47-3.33 (m, 2H), 3.05 (s, 3H) ppm; ES-MS m/z 494 (MH<sup>+</sup>).

20

173

**Example 85**

**4-((*E*)-{[1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone}methyl)-*N*-(3-pyrrolidin-1-ylpropyl)benzamide**



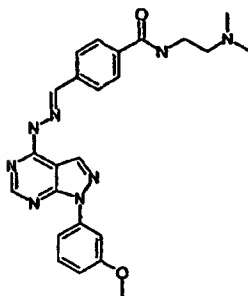
To a solution of 4-((*E*)-{[1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone}methyl)benzoic acid (Example 83) (100 mg, 0.26 mmol) in DMF (4 mL),  
10 was added 3-pyrrolidin-1-ylpropan-1-amine (0.13 mL, 1.03 mmol),  
diethylcyanophosphonate (0.16 mL, 1.03 mmol), and triethylamine (0.11 mL, 0.77 mmol). The solution was stirred at RT for 3 h, then water and diethyl ether were added. The resulting precipitate was collected by filtration to give pure product (86  
15 mg, yield 66%).

<sup>1</sup>H NMR (300 MHz, DMSO) δ 12.49–12.21 (s br, 1H), 8.68 (s, 1H), 8.65 (t, 1H), 8.52 (s, 1H), 8.35 (s, 1H), 7.95–7.84 (m, 6H), 7.48 (t, 1H), 6.95 (dd, 1H), 3.84 (s, 3H), 3.40–3.28 (m, 2H), 2.55–2.39 (m, 6H), 1.75–1.63 (m, 6H) ppm; ES-MS *m/z* 499 (MH<sup>+</sup>).

20

**Example 86**

*N*-[2-(Dimethylamino)ethyl]-4-((*E*)-{[1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazono}methyl)benzamide hydrochloride

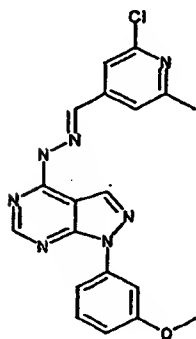
5     $\text{Cl}^-$ 

Prepared from 4-((*E*)-{[1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazono}methyl)benzoic acid (Example 83) using the general procedure for *N*-[2-(dimethylamino)ethyl]-4-((*E*)-{[1-(3-propylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazono}methyl)benzamide (Example 51).

<sup>1</sup>H NMR (300 MHz, DMSO)  $\delta$  10.20 (s, 1H), 8.96 (s, 1H), 8.67 (s, 1H), 8.51 (s, 1H), 8.36 (s, 1H), 8.02 (d, 2H), 7.92 (d, 2H), 7.87-7.83 (m, 2H), 7.47 (t, 1H), 6.94 (d, 1H), 3.83 (s, 3H), 3.64 (m, 2H), 3.72 (m, 2H), 2.81 (s, 6H) ppm.

**Example 87**

**2-Chloro-6-methylisonicotinaldehyde [1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone**

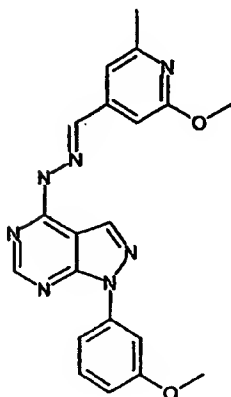


5

Prepared from 4-hydrazino-1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine (Intermediates Example T) and 2-chloro-6-methylisonicotinaldehyde using the  
10 general procedure for nicotinaldehyde [1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone (Example 72).

<sup>1</sup>H NMR (300 MHz, DMSO) δ 12.51 (s, 1H), 8.68 (s, 1H), 8.57 (s, 1H), 8.23 (s, 1H), 7.91-7.86 (m, 2H), 7.67 (s, 1H), 6.62 (s, 1H), 7.50 (t, 1H), 6.97 (d, 1H), 3.87 (s, 3H), 2.57 (s, 3H)  
15 ppm; ES-MS m/z 392 (MH<sup>+</sup>).



**Example 88****2-Methoxy-6-methylisonicotinaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone**

A mixture of 2-chloro-6-methylisonicotinaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone (Example 87) (0.15 g; 0.38 mmol) and sodium methoxide (0.206 g; 3.81 mmol) in DMSO (10 mL) were heated to 105 °C for 24h. The solution was cooled to RT then water (50 mL) and ethylacetate (50 mL) were added. The organic layer was separated, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to give the title compound (54 mg) as a off-white powder (37%).

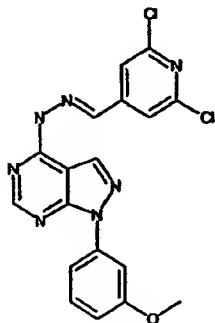
15

<sup>1</sup>H NMR (300 MHz, DMSO) δ 12.36 (s, 1H), 8.54 (s, 1H), 8.49 (s, 1H), 8.13 (s, 1H), 7.84 (d, 1H), 7.81 (s, 1H), 7.44 (t, 1H), 7.19 (s, 1H), 6.91 (d, 1H), 6.80 (s, 1H), 3.84 (s, 3H), 3.81 (s, 3H), 2.44 (s, 3H) ppm; ES-MS m/z 388 (MH<sup>+</sup>).

20

**Example 89**

**2,6-Dichloroisonicotinaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone**



5

Prepared from 4-hydrazino-1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (Intermediates Example T) and 2,6-dichloroisonicotinaldehyde using the general procedure for nicotinaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone (Example 72).

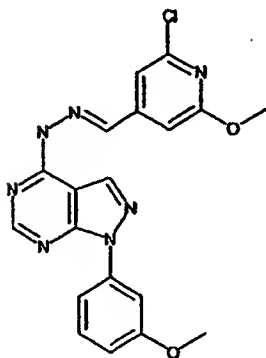
10

<sup>1</sup>H NMR (300 MHz, DMSO) δ 12.66 (s, 1H), 8.58 (s, 1H), 8.54 (s, 1H), 8.18 (s, 1H), 7.84-7.80 (m, 4H), 7.44 (t, 1H), 6.92 (d, 1H), 3.82 (s, 3H) ppm.

15

**Example 90**

**2-chloro-6-methoxyisonicotinaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone**

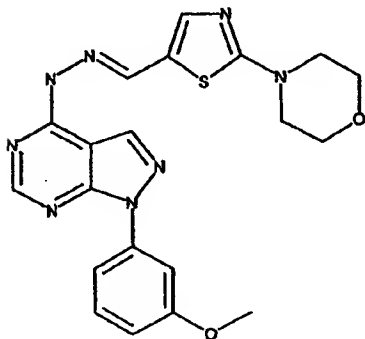


A mixture of 2,6-dichloroisonicotinaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone (Example 89) (0.060 g; 0.15 mmol) and sodium methoxide  
10 (0.15 g; 2.78 mmol) in DMSO (5 mL) were heated to 105 °C for 1h. The solution was cooled to RT then 1N HCl (5 mL) and ethylacetate (50 mL) were added. The organic layer was separated, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give the title compound (37 mg; 60%).

15 <sup>1</sup>H NMR (300 MHz, DMSO) δ 12.59 (s, 1H), 8.55 (m, 2H), 8.19 (s, 1H), 7.83-7.81 (m, 2H), 7.48-7.44 (m, 2H), 7.12 (s, 1H), 6.93 (d, 1H), 3.88 (s, 3H), 3.82 (s, 3H) ppm; ES-MS *m/z* 408.5 (MH<sup>+</sup>).

**Example 91**

**2-Morpholin-4-yl-1,3-thiazole-5-carbaldehyde [1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone**



Prepared from 4-hydrazino-1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine (Intermediates Example T) and 2-morpholin-4-yl-1,3-thiazole-5-carbaldehyde using the general procedure for nicotinaldehyde [1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone (Example 72).

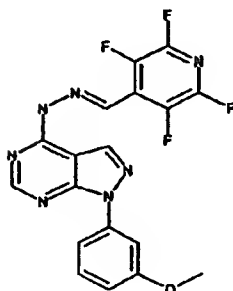
10

<sup>1</sup>H NMR (300 MHz, DMSO) δ 12.24 (s, 1H), 8.47-2.46 (m, 2H), 8.36 (s, 1H), 7.91-7.85 (m, 2H), 7.66 (s, 1H), 7.49 (t, 1H), 6.96 (d, 1H), 3.86 (s, 3H), 3.76 (m, 4H), 3.57 (m, 4H) ppm;

15 ES-MS m/z 435.6 (MH<sup>+</sup>).

**Example 92**

**2,3,5,6-Tetrafluoroisonicotinaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone**

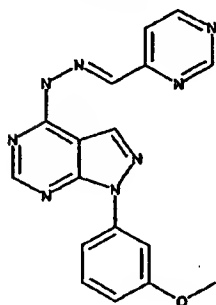


Prepared from 4-hydrazino-1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (Intermediates Example T) and 2,3,5,6-tetrafluoroisonicotinaldehyde using the general procedure for nicotinaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone (Example 72).

10

<sup>1</sup>H NMR (300 MHz, DMSO) δ 12.72 (s, 1H), 8.58 (s, 1H), 8.42 (s, 1H), 8.30 (s, 1H), 7.82-7.78 (m, 2H), 7.44 (t, 1H), 6.92 (d, 1H), 3.82 (s, 3H) ppm.

15

Example 93Pyrimidine-4-carbaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone

5

Prepared from 4-hydrazino-1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (Intermediates Example T) and pyrimidine-4-carbaldehyde using the general procedure for nicotinaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone (Example 72).

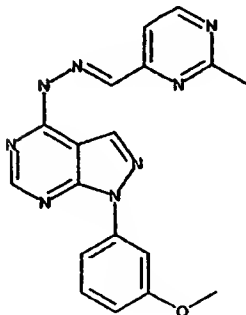
10

<sup>1</sup>H NMR (300 MHz, DMSO) δ 12.60 (s, 1H), 9.21 (s, 1H), 8.85 (d, 1H), 8.70 (s, 1H), 8.55 (s, 1H), 8.20 (s, 1H), 8.13 (d, 1H), 7.84–7.82 (m, 2H), 7.45 (t, 1H), 6.92 (d, 1H), 3.82 (s, 3H) ppm; ES-MS *m/z* 345.3 (MH<sup>+</sup>).

15

**Example 94**

**2-Methylpyrimidine-4-carbaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone**



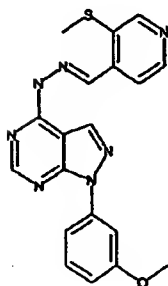
5

Prepared from 4-hydrazino-1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (Intermediates Example T) and 2-methylpyrimidine-4-carbaldehyde using the general  
10 procedure for nicotinaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone (Example 72).

<sup>1</sup>H NMR (300 MHz, DMSO) δ 12.73 (s, 1H), 8.80 (d, 1H), 8.76 (s, 1H), 8.62 (s, 1H), 8.22 (s,  
1H), 8.00 (d, 1H), 7.91-7.87 (m, 2H), 7.51 (t, 1H), 6.99 (d, 1H), 3.87 (s, 3H), 2.68 (s, 3H)  
15 ppm.

Example 953-(Methylthio)isonicotinaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone

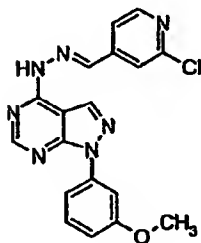
5



- 10 Prepared from 4-hydrazino-1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (Intermediates Example T) and 3-(methylthio)isonicotinaldehyde using the general procedure for nicotinaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone (Example 72).
- 15 <sup>1</sup>H NMR (300 MHz, DMSO) δ 12.54 (s, 1H), 8.70 (s, 1H), 8.66 (s, 1H), 8.63 (s, 1H), 8.55 (s, 1H), 8.49 (d, 1H), 7.90 (d, 1H), 7.85-7.82 (m, 2H), 7.46 (t, 1H), 6.94 (d, 1H), 3.82 (s, 3H), 2.60 (s, 3H) ppm; ES-MS *m/z* 390 (MH<sup>+</sup>).

20



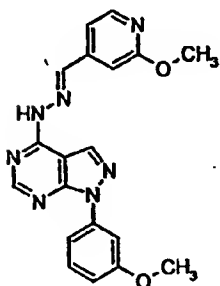
**Example 96****2-Chloroisonicotinaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone**

5

Prepared from 4-hydrazino-1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (Intermediates Example T) and 2-chloroisonicotinaldehyde using the general procedure for nicotinaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone (Example 72).

<sup>1</sup>H NMR (300 MHz, DMSO)  $\delta$  12.57 (s, 1H), 8.68 (s, 1H), 8.58 (s, 1H), 8.49 (d, 1H), 8.27 (s, 1H), 7.98-7.79 (m, 4H), 7.48 (t, 1H), 6.95 (d, 1H), 3.84 (s, 3H) ppm; ES-MS *m/z* 381 (MH<sup>+</sup>).

15

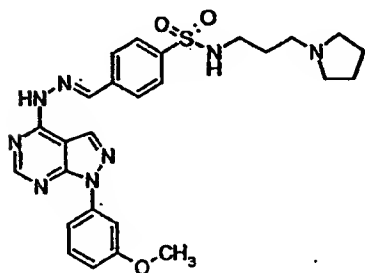
**Example 97****2-Methoxyisonicotinaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone**

Added sodium methoxide (50 mg) to a solution of 2-chloroisonicotinaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone (Example 96) (50mg, 0.13 mmol) in DMSO (2 ml). The mixture was stirred at 80°C for 1h, cooled to RT and water was added. The resulting solid was collect by filtration, washed with water, and air dried to give pure product (33 mg, yield 68%).

15 <sup>1</sup>H NMR (300 MHz, DMSO) δ 12.51 (s, 1H), 8.63 (s, 1H), 8.27-8.23 (m, 2H), 7.90-7.83 (m, 2H), 7.51-7.45 (m, 2H), 7.10 (s, 1H), 6.99-6.93 (m, 1H), 3.90 (s, 3H), 3.84 (s, 3H) ppm; ES-MS m/z 376 (MH<sup>+</sup>).

Example 98

4-((*E*)-{[1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazono}methyl)-*N*-(3-pyrrolidin-1-ylpropyl)benzenesulfonamide



Prepared from 4-hydrazino-1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (Intermediates Example T) and 4-formyl-*N*-(3-pyrrolidin-1-

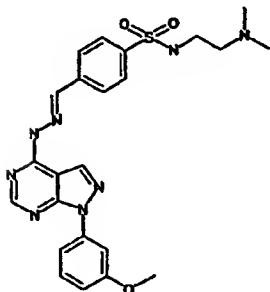
10 ylpropyl)benzenesulfonamide using the general procedure for nicotinaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone (Example 72).

<sup>1</sup>H NMR (300 MHz, DMSO) δ 12.44 (s, 1H), 8.70 (s, 1H), 8.54 (s, 1H), 8.37 (s, 1H), 8.06 (d, 2H), 7.88 (t, 5H), 7.49 (t, 1H), 6.95 (dd, 1H), 3.84 (s, 3H), 3.40-3.28 (m, 2H) 3.06-2.95

15 (m, 4H) 2.94-2.75 (m, 2H), 1.92-1.63 (m, 6H) ppm; ES-MS *m/z* 535 (MH<sup>+</sup>).

Example 99

*N*-[2-(Dimethylamino)ethyl]-4-((*E*)-{[1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazono}methyl)benzenesulfonamide



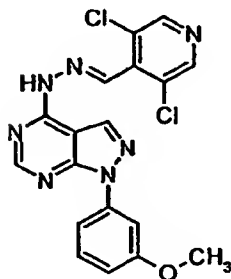
5

- Prepared from 4-hydrazino-1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (Intermediates Example T) and *N*-[2-(dimethylamino)ethyl]-4-formylbenzenesulfonamide (Intermediates Example U) using the general procedure for nicotinaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone (Example 72).
- <sup>1</sup>H NMR (300 MHz, DMSO) δ 12.51 (s, 1H), 10.09 (s, 1H), 8.73 (s, 1H), 8.58 (s, 1H), 8.42 (s, 1H), 8.20 (m, 1H), 8.09 (d, 2H), 7.98 (d, 2H), 7.75 (d, 1H), 7.52 (t, 1H), 7.00 (d, 1H), 3.87 (s, 3H), 3.18 (s br, 4H), 2.79 (s, 6H) ppm; ES-MS *m/z* 493 (MH<sup>+</sup>).

15

**Example 100**

**3,5-Dichloroisonicotinaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone**

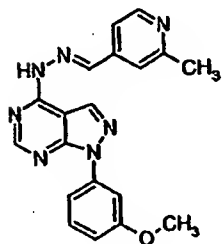


5

- Prepared from 4-hydrazino-1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (Intermediates Example T) and 3,5-dichloroisonicotinaldehyde using the general procedure for nicotinaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone (Example 72).

- <sup>1</sup>H NMR (300 MHz; DMSO) δ 8.74 (s, 2H), 8.58 (s, 2H), 8.56 (s, 1H), 7.84-7.78 (m, 2H), 7.46 (t, 1H), 6.94 (d, 1H), 3.82 (s, 3H) ppm; ES-MS *m/z* 414 (MH<sup>+</sup>).

15

Example 1012-Methylisonicotinaldehyde [1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone

5

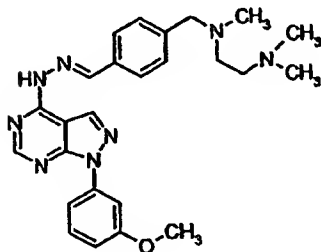
- Prepared from 4-hydrazino-1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine (Intermediates Example T) and 2-methylisonicotinaldehyde using the general procedure for nicotinaldehyde [1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone (Example 72).

<sup>1</sup>H NMR (300 MHz, DMSO) δ 12.51 (s, 1H), 8.72 (s, 1H), 8.58 (s, 2H), 8.27 (s, 1H), 7.92-7.85 (m, 2H), 7.65-7.60 (m, 2H), 7.51 (t, 1H), 7.00 (dd, 1H), 3.87 (s, 3H), 3.35 (s, 3H) ppm;  
ES-MS m/z 360 (MH<sup>+</sup>).

15

**Example 102**

**4-{[[2-(Dimethylamino)ethyl](methyl)amino]methyl}benzaldehyde [1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone**



5

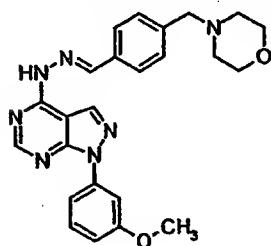
- Prepared from 4-hydrazino-1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine (Intermediates Example T) and 4-{[[2-(dimethylamino)ethyl](methyl)amino]methyl}benzaldehyde using the general procedure for nicotinaldehyde [1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone (Example 72).

- <sup>1</sup>H NMR (300 MHz, DMSO) δ 12.23 (s, 1H), 8.66 (s, 1H), 8.50 (s, 1H), 8.30 (s, 1H), 7.90-7.87 (m, 2H), 7.78 (d, 2H), 7.51-7.40 (m, 3H), 6.95 (dd, 1H), 3.85 (s, 3H), 3.53 (s, 2H), 2.55-2.39 (m, 4H), 2.14 (d, 9H) ppm; ES-MS m/z 459 (MH<sup>+</sup>).

15

**Example 103**

**4-(Morpholin-4-ylmethyl)benzaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone**



5

Prepared from 4-hydrazino-1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (Intermediates Example T) and 4-(morpholin-4-ylmethyl)benzaldehyde using the general procedure for nicotinaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone (Example 72).

10

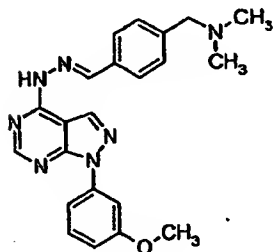
<sup>1</sup>H NMR (300 MHz, DMSO) δ 12.25 (s, 1H), 8.66 (s, 1H), 8.50 (s, 1H), 8.30 (s, 1H), 7.90-7.84 (m, 2H), 7.79 (d, 2H), 7.51-7.40 (m, 3H), 6.95 (dd, 1H), 3.85 (s, 3H), 3.61-3.56 (m, 4H), 3.52 (s, 2H) 2.40-2.34 (m, 4H) ppm; ES-MS *m/z* 444 (MH<sup>+</sup>).

15



**Example 104**

**4-[[[(Dimethylamino)methyl]benzaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone**

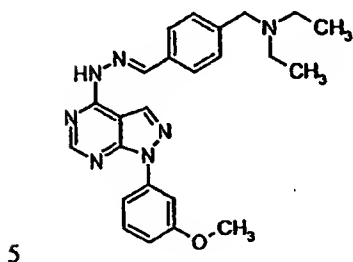


Prepared from 4-hydrazino-1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (Intermediates Example T) and 4-[[[(dimethylamino)methyl]benzaldehyde using the  
10 general procedure for nicotinaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone (Example 72).

<sup>1</sup>H NMR (300 MHz, DMSO) δ 12.24 (s, 1H), 8.66 (s, 1H), 8.50 (s, 1H), 8.30 (s, 1H), 7.90-  
7.84 (m, 2H), 7.78 (d, 2H), 7.51-7.40 (m, 3H), 6.95 (dd, 1H), 3.85 (s, 3H), 3.44 (s, 2H)  
15 2.16 (s, 6H) ppm; ES-MS *m/z* 402 (MH<sup>+</sup>).

**Example 105**

**4-[(Diethylamino)methyl]benzaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone**

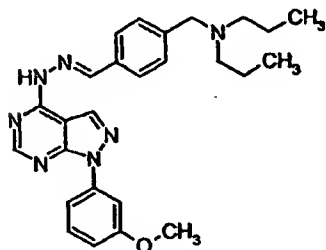


Prepared from 4-hydrazino-1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (Intermediates Example T) and 4-[(diethylamino)methyl]benzaldehyde using the  
10 general procedure for nicotinaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone (Example 72).

<sup>1</sup>H NMR (300 MHz, DMSO) δ 12.24 (s, 1H), 8.66 (s, 1H), 8.50 (s, 1H), 8.30 (s, 1H), 7.90-7.84 (m, 2H), 7.78 (d, 2H), 7.51-7.40 (m, 3H), 6.95 (dd, 1H), 3.85 (s, 3H), 3.58 (s, 2H),  
15 2.48 (q, 4H), 0.99 (t, 6H) ppm; ES-MS *m/z* 430 (MH<sup>+</sup>).

Example 106

4-[(Dipropylamino)methyl]benzaldehyde [1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone



5

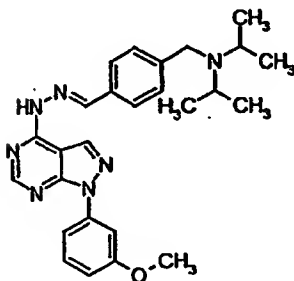
Prepared from 4-hydrazino-1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine (Intermediates Example T) and 4-[(dipropylamino)methyl]benzaldehyde using the general procedure for nicotinaldehyde [1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone (Example 72).

<sup>1</sup>H NMR (300 MHz, DMSO) δ 12.21 (s, 1H), 8.67 (s, 1H), 8.50 (s, 1H), 8.30 (s, 1H), 7.90-7.84 (m, 2H), 7.78 (d, 2H), 7.51-7.40 (m, 3H), 6.95 (dd, 1H), 3.85 (s, 3H), 3.56 (s, 2H), 2.35 (t, 4H), 1.43 (q, 4H), 0.83 (t, 6H) ppm; ES-MS m/z 458 (MH<sup>+</sup>).

15

**Example 107**

**4-[(Diisopropylamino)methyl]benzaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone**



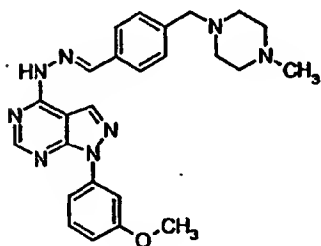
5

Prepared from 4-hydrazino-1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (Intermediates Example T) and 4-[(diisopropylamino)methyl]benzaldehyde using the  
10 general procedure for nicotinaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone (Example 72).

<sup>1</sup>H NMR (300 MHz, DMSO) δ 12.21 (s, 1H), 8.66 (s, 1H), 8.49 (s, 1H), 8.29 (s, 1H), 7.88-  
7.84 (m, 2H), 7.75 (d, 2H), 7.51-7.43 (m, 3H), 6.95 (dd, 1H), 3.84 (s, 3H), 3.66 (s, 2H),  
15 2.98 (quin, 2H), 0.99 (d, 12H) ppm; ES-MS *m/z* 428 (MH<sup>+</sup>).

**Example 108**

**4-[[4-Methylpiperazin-1-yl)methyl]benzaldehyde [1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone**



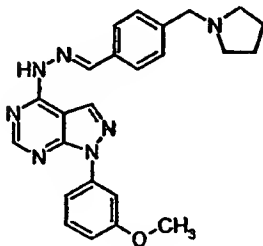
Prepared from 4-hydrazino-1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine (Intermediates Example T) and 4-[[4-methylpiperazin-1-yl)methyl]benzaldehyde (Intermediates Example W) using the general procedure for nicotinaldehyde [1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone (Example 72).

10

<sup>1</sup>H NMR (300 MHz, DMSO) δ 12.22 (s, 1H), 8.65 (s, 1H), 8.50 (s, 1H), 8.30 (s, 1H), 7.88-7.84 (m, 2H), 7.78 (d, 2H), 7.51-7.40 (m, 3H), 6.95 (dd, 1H), 3.84 (s, 3H), 3.50 (s, 2H), 2.45-2.56 (m, 6H), 2.15 (s, 3H) ppm; ES-MS m/z 457 (MH<sup>+</sup>).

**Example 109**

**4-(Pyrrolidin-1-ylmethyl)benzaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone**

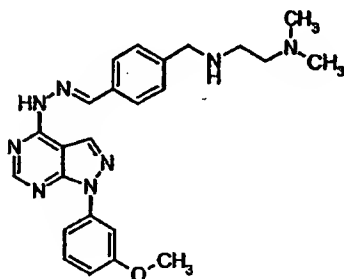


Prepared from 4-hydrazino-1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (Intermediates Example T) and 4-(pyrrolidin-1-ylmethyl)benzaldehyde (Intermediates  
10 Example X) using the general procedure for nicotinaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone (Example 72).

<sup>1</sup>H NMR (300 MHz, DMSO) δ 12.24 (s, 1H), 8.65 (s, 1H), 8.50 (s, 1H), 8.30 (s, 1H), 7.90-  
7.84 (m, 2H), 7.78 (d, 2H), 7.51-7.40 (m, 3H), 6.95 (dd, 1H), 3.84 (s, 3H), 3.62 (s, 2H),  
15 2.47-2.56 (m, 4H), 1.65-1.81 (m, 4H) ppm; ES-MS *m/z* 428 (MH<sup>+</sup>).

**Example 110**

**4-({[2-(Dimethylamino)ethyl]amino}methyl)benzaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone**



5

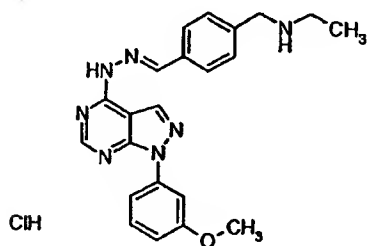
A mixture of 4-hydrazino-1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (Intermediates Example T) (25 mg, 0.10 mmol), *N*'-[4-(diethoxymethyl)benzyl]-*N*<sup>2</sup>,*N*<sup>2</sup>-dimethylethane-1,2-diamine (Intermediates Example Y) (27 mg, 0.10 mmol), and 6N HCl (5 mL) was stirred at 50°C for 2h. Cooled mixture to RT, and filtered. Resulting solid was partitioned between 1N NaOH and ethylacetate. The organic layer was dried over sodium sulfate, and concentrated to give product (16 mg, 37% yield).

<sup>1</sup>H NMR (300 MHz, DMSO) δ 8.64 (s, 1H), 8.48 (s, 1H), 8.28 (s, 1H), 7.88-7.80 (m, 2H), 7.76 (d, 2H), 7.51-7.40 (m, 3H), 6.93 (dd, 1H), 3.83 (s, 3H), 3.74 (s, 2H), 2.60-2.52 (m, 2H), 2.36-2.29 (m, 2H), 2.10 (s, 6H) ppm; ES-MS *m/z* 445 (MH<sup>+</sup>).

20

Example 1114-[[[(Ethylamino)methyl]benzaldehyde [1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone hydrochloride

5



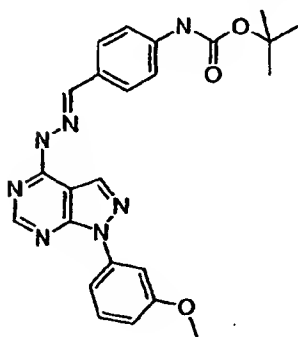
- A mixture of 4-hydrazino-1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine (Intermediates Example T) (50 mg, 0.19 mmol), N-[4-(diethoxymethyl)benzyl] ethanamine (Intermediates Example Z) (45 mg, 0.19 mmol) and 6N HCl (5 mL) was stirred at 50°C for 16h. The cooled solution was filtered to collect the product as a white solid (58mg, 70% yield).
- <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OH) δ 8.66 (s, 1H), 8.64 (s, 1H), 8.61 (s, 1H), 8.15 (d, 2H), 7.75-7.69 (m, 4H), 7.51 (t, 1H), 7.07 (dd, 1H), 4.31 (s, 2H), 3.91 (s, 3H), 3.18 (q, 2H), 1.38 (t, 3H) ppm; ES-MS m/z 402 (MH<sup>+</sup>).

20



Example 112

*tert*-Butyl 4-(((*E*)-{[1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazono} methyl)phenyl)carbamate



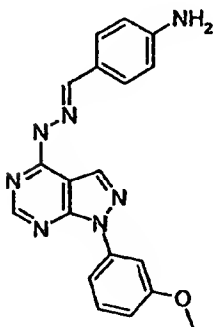
5

A mixture of 4-hydrazino-1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (Intermediates Example T) (87.5 mg, 0.342 mmol), *tert*-butyl 4-

- 10 formylphenylcarbamate (151 mg 0.683 mmol) and pyrrolidine (2 drops) in ethanol (20 mL) was heated to 100 °C for 21 h. The reaction was then cooled to RT, and the solid collected by filtration and washed with ethanol and ether to provide product as a yellow solid (133 mg, 85% yield).

- 15 <sup>1</sup>H NMR (400 MHz, DMSO): δ 12.16 (s, 1H), 9.63 (s, 1H), 8.64 (s, 1H), 8.46 (s, 1H), 8.21 (s, 1H), 7.86 (d, 2H), 7.72 (d, 2H), 7.58 (d, 2H), 7.46 (t, 1H), 6.93 (d, 1H), 3.83 (s, 3H), 1.48 (s, 9H) ppm; ES-MS *m/z* 460 (MH<sup>+</sup>).

20

**Example 113****4-Aminobenzaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone**

5

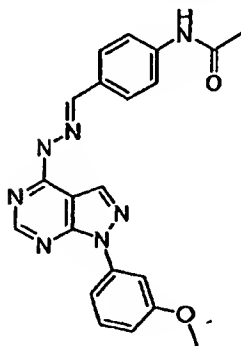
A mixture of *tert*-butyl 4-((*E*)-{[1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone}methyl)phenylcarbamate (Example 112) (602 mg, 1.311 mmol) and 20% trifluoroacetic acid in dichloromethane (10 mL) was stirred at RT for 18 h. The reaction mixture was partitioned between dichloromethane and satd. aq. NaHCO<sub>3</sub>, and the organic layer was dried (MgSO<sub>4</sub>) and concentrated to provide product as a yellow solid (433 mg, 92% yield).

<sup>1</sup>H NMR (400 MHz, DMSO): δ 11.93 (s, 1H), 8.60 (s, 1H), 8.40 (s, 1H), 8.10 (s, 1H), 7.85 (m, 2H), 7.46 (m, 3H), 6.92 (d, 1H), 6.63 (d, 2H), 5.70 (broad s, 2H), 3.82 (s, 3H) ppm; ES-MS *m/z* 360 (MH<sup>+</sup>).

20

Example 114

*N*-[4-((*E*)-{2-[1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazono}methyl)phenyl]acetamide



5

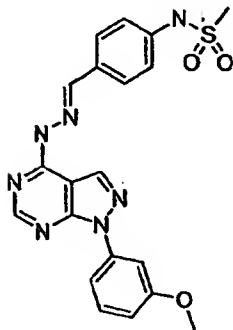
A mixture of 4-hydrazino-1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (Intermediates Example T) (150 mg, 0.585 mmol), *N*-(4-formylphenyl)acetamide (190 mg 1.17 mmol) and pyrrolidine (2 drops) in ethanol (25 mL) was heated to 100 °C for 21 h. The reaction was then cooled to RT, the solid collected by filtration, and washed with ethanol and ether to provide product as a white solid (150 mg, 64% yield).

<sup>1</sup>H NMR (400 MHz, DMSO): δ 12.18 (s, 1H), 10.16 (s, 1H), 8.66 (s, 1H), 8.47 (s, 1H), 8.22 (s, 1H), 7.85 (m, 2H), 7.73 (dd, 4H), 7.46 (t, 1H), 6.93 (dd, 1H), 3.83 (s, 3H), 2.06 (s, 3H) ppm; ES-MS *m/z* 402 (MH<sup>+</sup>).

15

**Example 115**

*N*-[4-[(*E*)-{2-[1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazono}methyl]phenyl]methanesulfonamide



A mixture of 4-hydrazino-1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine  
10 (Intermediates Example T) (43 mg, 0.167 mmol), *N*-(4-formylphenyl)methanesulfonamide (40 mg 0.201 mmol) and pyrrolidine (2 drops) in ethanol (10 mL) was heated to 100 °C for 21 h. The reaction was then cooled to RT, the solid collected by filtration, and washed with ethanol and ether to provide product as a white solid (67 mg, 92% yield).

15

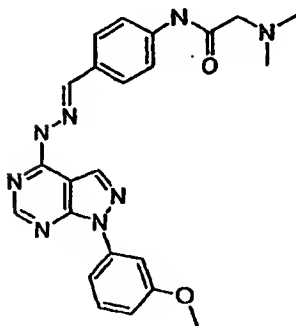
<sup>1</sup>H NMR (400 MHz, DMSO) δ 12.22 (s, 1H), 10.08 (s, 1H), 8.66 (s, 1H), 8.47 (s, 1H), 8.24 (s, 1H), 7.82 (m, 4H), 7.47 (t, 1H), 7.31 (d, 2H), 6.94 (d, 1H), 3.83 (s, 3H), 3.06 (s, 3H) ppm; ES-MS *m/z* 438 (MH<sup>+</sup>).

20

Example 116

*N'*-[4-[(*E*)-{[1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazono}methyl]phenyl]-*N*<sup>*R*</sup>,*N*<sup>*R*</sup>-dimethylglycinamide

5



10

A mixture of 4-hydrazino-1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (Intermediates Example T) (109 mg, 0.428 mmol), *N'*-(4-formylphenyl)-*N*<sup>*R*</sup>,*N*<sup>*R*</sup>-dimethylglycinamide (Intermediates Example AA) (106 mg 0.514 mmol) and pyrrolidine (2 drops) in ethanol (20 mL) was heated to 100 °C for 21 h. The reaction was then cooled to RT, the solid collected by filtration, and washed with ethanol and ether to provide product as a yellow solid (151 mg, 79% yield).

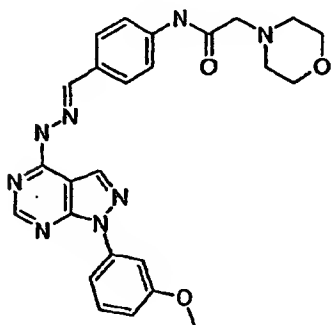
15

<sup>1</sup>H NMR (400 MHz, DMSO): δ 12.21 (s, 1H), 9.97 (s, 1H), 8.67 (s, 1H), 8.48 (s, 1H), 8.25 (s, 1H), 7.83 (m, 6H), 7.48 (t, 1H), 6.95 (dd, 1H), 3.84 (s, 3H), 3.10 (s, 2H), 2.28 (s, 6H) ppm; ES-MS *m/z* 445 (MH<sup>+</sup>).

20

**Example 117**

*N*-[4-(((*E*)-{[1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazono}methyl)phenyl]-2-morpholin-4-ylacetamide



5

A mixture of 4-hydrazino-1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (Intermediates Example T) (77 mg, 0.301 mmol), *N*-(4-formylphenyl)-2-morpholin-4-ylacetamide (Intermediates Example BB) (112 mg 0.452 mmol) and pyrrolidine (2 drops) in ethanol (15 mL) was heated to 100 °C for 18h. The reaction was then cooled to RT, the solid collected by filtration, and washed with ethanol and ether to provide product as a light yellow solid (114 mg, 78% yield).

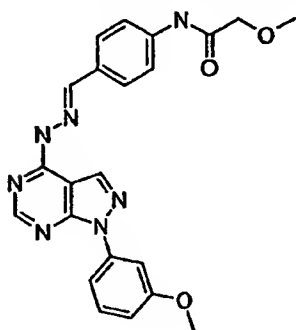
15

<sup>1</sup>H NMR (400 MHz, DMSO): δ 12.19 (s, 1H), 9.97 (s, 1H), 8.65 (s, 1H), 8.46 (s, 1H), 8.23 (s, 1H), 7.85 (dd, 2H), 7.77 (s, 4H), 7.46 (t, 1H), 6.92 (dd, 1H), 3.82 (s, 3H), 3.62 (t, 4H), 3.14 (s, 2H), 2.50 (t, 4H) ppm; ES-MS *m/z* 487 (MH<sup>+</sup>).

20

**Example 118**

**2-Methoxy-N-[4-[(E)-{[1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazono} methyl]phenyl]acetamide**



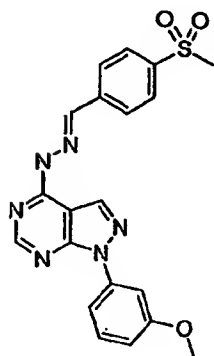
5

A mixture of 4-hydrazino-1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine (Intermediates Example T) (152 mg, 0.595 mmol), N-(4-formylphenyl)-2-methoxyacetamide (Intermediates Example CC) (160 mg 0.893 mmol) and pyrrolidine  
 10 (2 drops) in ethanol (20 mL) was heated to 100 °C for 18 h. The reaction was then cooled to RT, the solid collected by filtration, and washed with ethanol and ether to provide product as an orange solid (236 mg, 91% yield).

<sup>1</sup>H NMR (400 MHz, DMSO): δ 12.18 (s, 1H), 9.99 (s, 1H), 8.66 (s, 1H), 8.46 (s, 1H), 8.23  
 15 (s, 1H), 7.80 (m, 6H), 7.46 (t, 1H), 6.92 (d, 1H), 4.01 (s, 3H), 3.82 (s, 3H), 3.36 (s, 2H)  
 ppm; ES-MS m/z 432 (MH<sup>+</sup>).

Example 1194-(Methylsulfonyl)benzaldehyde [1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone

5



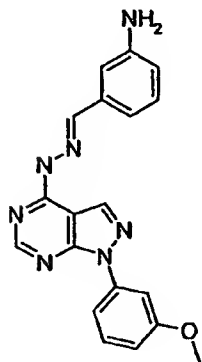
10 A mixture of 4-hydrazino-1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine (Intermediates Example T) (100 mg, 0.390 mmol), 4-(methylsulfonyl) benzaldehyde (108 mg 0.585 mmol) and pyrrolidine (2 drops) in ethanol (20 mL) was heated to 100 °C for 3.5 h. The reaction was then cooled to RT, the solid collected by filtration, and washed with ethanol and ether to provide product as a light yellow solid (142 mg, 86% yield).

15

<sup>1</sup>H NMR (400 MHz, DMSO) δ 12.48 (s, 1H), 8.68 (s, 1H), 8.53 (s, 1H), 8.37 (s, 1H), 8.08 (d, 2H), 8.00 (d, 2H), 7.84 (m, 2H), 7.47 (t, 1H), 6.94 (dd, 1H), 5.73 (s, 3H), 3.83 (s, 3H) ppm; ES-MS m/z 423 (MH<sup>+</sup>).

20



**Example 120****3-aminobenzaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone**

5

A mixture of 4-hydrazino-1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine

(Intermediates Example T) (200 mg, 0.780 mmol), 3-aminobenzaldehyde (189 mg

10 1.560 mmol) and pyrrolidine (2 drops) in ethanol (20 mL) was heated to 100 °C for 3.5

h. The reaction was then cooled to RT, the solid collected by filtration, and washed

with ethanol and ether to provide product as a light brown solid (209 mg, 75% yield).

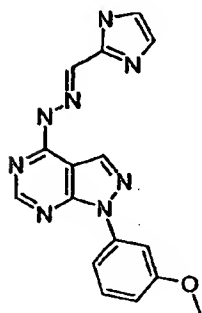
<sup>1</sup>H NMR (400 MHz, DMSO): δ 12.13 (s, 1H), 8.66 (s, 1H), 8.47 (s, 1H), 8.13 (s, 1H), 7.86

15 (m, 2H), 7.46 (t, 1H), 7.11 (m, 2H), 6.93 (d, 1H), 6.81 (d, 1H), 6.63 (d, 1H), 5.34 (s, 2H),

3.82 (s, 3H) ppm; ES-MS m/z 360 (MH<sup>+</sup>).

Example 1211*H*-imidazole-2-carbaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone

5



A mixture of 4-hydrazino-1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (Intermediates Example T) (100 mg, 0.390 mmol), 1*H*-imidazole-2-carbaldehyde (75  
 10 mg 0.780 mmol) and pyrrolidine (2 drops) in ethanol (10 mL) was heated to 100 °C for 5 h. The reaction was then cooled to RT, the solid collected by filtration, and washed with ethanol and ether to provide product as a brown solid (72 mg, 55% yield).

<sup>1</sup>H NMR (400 MHz, DMSO) δ 12.74 (s, 1H), 12.21 (s, 1H), 9.08 (s, 1H), 8.49 (s, 1H), 8.22

15 (s, 1H), 7.86 (m, 2H), 7.47 (t, 1H), 7.39 (s, 1H), 7.13 (s, 1H), 6.94 (dd, 1H), 3.84 (s, 3H)

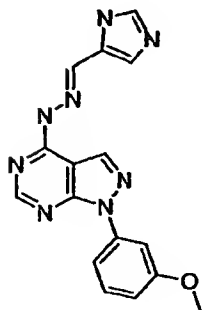
ppm; ES-MS *m/z* 335 (MH<sup>+</sup>).

210

Example 122

1*H*-imidazole-5-carbaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone

5



10

A mixture of 4-hydrazino-1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (Intermediates Example T) (100 mg, 0.390 mmol), 1*H*-imidazole-5-carbaldehyde (75 mg 0.780 mmol) and pyrrolidine (2 drops) in ethanol (10 mL) was heated to 100 °C for 18 h. The reaction was then cooled to RT, the solid collected by filtration, and washed

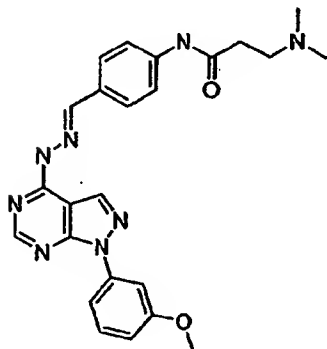
15 with ethanol and ether to provide product as a brown solid (67 mg, 51% yield).

<sup>1</sup>H NMR (400 MHz, DMSO) δ 12.91 (s, 1H), 8.57 (s, 1H), 8.47 (s, 1H), 8.11 (s, 1H), 7.84 (m, 3H), 7.61 (s, 1H), 7.46 (t, 1H), 6.93 (dd, 1H), 5.75 (s, 1H), 3.83 (s, 3H) ppm; ES-MS m/z 336 (MH<sup>+</sup>).

20

**Example 123**

*N'*-[4-(((*E*)-{[1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)hydrazono}methyl)phenyl]-*N*<sup>*P*</sup>,*N*<sup>*P*</sup>-dimethyl-*D*-alaninamide



5

A mixture of 4-hydrazino-1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (Intermediates Example T) (59 mg, 0.226 mmol), *N'*-(4-formylphenyl)-*N*<sup>*P*</sup>,*N*<sup>*P*</sup>-dimethyl-*D*-alaninamide (Intermediates Example DD) (100 mg 0.453 mmol) and pyrrolidine (2 drops) in ethanol (10 mL) was heated to 100 °C for 18 h. The reaction was then cooled to RT and concentrated. The residue was triturated with diethyl ether, and the solid collected by filtration and washed with diethyl ether to provide product as a brown solid (16.8 mg, 17% yield).

15

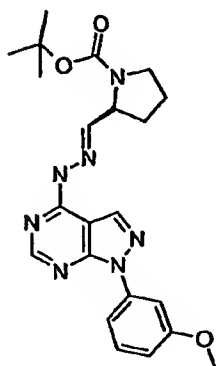
<sup>1</sup>H NMR (400 MHz, DMSO): δ 12.18 (s, 1H), 10.31 (s, 1H), 8.66 (s, 1H), 8.47 (s, 1H), 8.23 (s, 1H), 7.85 (m, 2H), 7.75 (m, 4H), 7.46 (t, 1H), 6.93 (dd, 1H), 3.83 (s, 3H), 2.77 (s, 2H), 2.49 (s, 6H), 1.69 (s, 2H) ppm; ES-MS *m/z* 460 (MH<sup>+</sup>).

20

**Example 124**

*tert*-Butyl (2*R*)-2-(((*E*)-{[1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazono}methyl)pyrrolidine-1-carboxylate

5



A mixture of 4-hydrazino-1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine  
10 (Intermediates Example T) (100 mg, 0.390 mmol), *tert*-butyl (2*S*)-2-formylpyrrolidine-1-carboxylate (90 mg 0.452 mmol) and pyrrolidine (2 drops) in ethanol (10 mL) was heated to 100 °C for 18 h. The reaction was then cooled to RT and concentrated. The residue was triturated with diethyl ether, and the solid collected by filtration and washed with diethyl ether to provide product (107 mg, 63% yield) as a yellow solid.

15

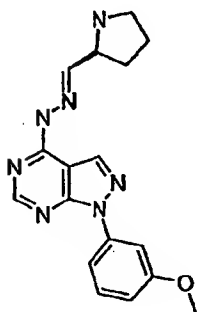
<sup>1</sup>H NMR (400 MHz, DMSO) δ 11.90 (s, 1H), 8.43 (s, 1H), 8.41 (s, 1H), 7.81 (m, 2H), 7.54 (m, 1H), 7.44 (t, 1H), 6.92 (d, 1H), 4.49 (d, 1H), 3.82 (s, 3H), 3.36 (m, 2H), 2.0 (m, 2H), 1.41 (m, 2H), 1.29 (s, 9H) ppm; ES-MS *m/z* 438 (MH<sup>+</sup>).

20

**Example 125**

(2*R*)-Pyrrolidine-2-carbaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone

5



10

A mixture of *tert*-butyl (2*R*)-2-((*E*)-{[1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone}methyl)pyrrolidine-1-carboxylate (Example 127) (80 mg, 0.182 mmol) and 20% trifluoroacetic acid in dichloromethane (10 mL) was stirred at RT for 18 h. The reaction mixture was partitioned between dichloromethane and satd. aq. NaHCO<sub>3</sub>. The organic layer was dried (MgSO<sub>4</sub>) and concentrated to provide product as a tan solid (49 mg, 80% yield).

<sup>1</sup>H NMR (400 MHz, DMSO) δ 11.98 (s, 1H), 8.48 (s, 1H), 8.44 (s, 1H), 7.84 (m, 2H), 7.52 (d, 1H), 7.46 (t, 1H), 6.94 (d, 1H), 3.84 (s, 3H), 3.16 (s, 1H), 2.88 (t, 2H), 1.98 (m, 1H),

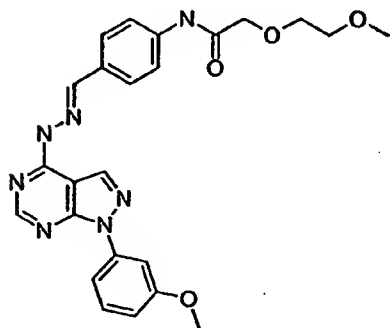
1.72 (m, 3H) ppm; ES-MS *m/z* 338 (MH<sup>+</sup>).

20

Example 126

2-(2-Methoxyethoxy)-N-[4-((E)-{1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl}hydrazono)methyl]phenyl]acetamide

5



- 10 A mixture of 4-hydrazino-1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine (Intermediates Example T) (38 mg, 0.147 mmol), N-(4-formylphenyl)-2-(2-methoxyethoxy)acetamide (Intermediates Example EE) (70 mg, 0.294 mmol) and pyrrolidine (2 drops) in ethanol (10 mL) was heated to 100 °C for 3 h. The reaction was then cooled to RT and concentrated. The residue was triturated with diethyl ether,
- 15 and the solid removed by filtration and washed with diethyl ether to provide product as a yellow solid (112 mg, 80% yield).

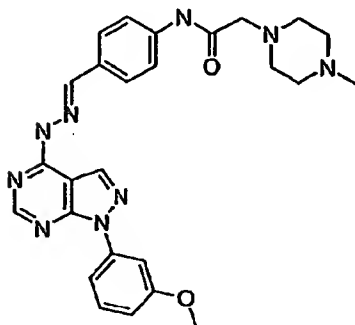
<sup>1</sup>H NMR (400 MHz, DMSO) δ 12.10 (s, 1H), 9.86 (s, 1H), 8.66 (s, 1H), 8.46 (s, 1H), 8.24 (s, 1H), 7.80 (m, 6H), 7.46 (t, 1H), 6.93 (d, 1H), 4.10 (s, 3H), 3.83 (s, 3H), 3.67 (t, 2H),

- 20 3.52 (t, 2H), 3.27 (s, 2H) ppm; ES-MS m/z 476 (MH<sup>+</sup>).

215

**Example 127**

*N*-[4-[(*E*)-{[1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazono}methyl]phenyl]-2-(4-methylpiperazin-1-yl)acetamide



5

A mixture of 4-hydrazino-1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (Intermediates Example T) (80 mg, 0.31 mmol), *N*-(4-formylphenyl)-2-(4-methylpiperazin-1-yl)acetamide (Intermediates Example FF) (162 mg, 0.62 mmol) and pyrrolidine (2 drops) in ethanol (10 mL) was heated to 100 °C for 18 h. The reaction was then cooled to RT and concentrated. The residue was triturated with diethyl ether, and the solid collected by filtration and washed with diethyl ether to provide product as a yellow solid (114 mg, 74% yield).

15

<sup>1</sup>H NMR (400 MHz, DMSO) δ 11.70 (s, 1H), 9.93 (s, 1H), 8.64 (s, 1H), 8.45 (s, 1H), 8.22 (m, 2H), 7.76 (d, 6H), 7.45 (t, 1H), 6.92 (d, 1H), 3.81 (s, 3H), 3.35 (m, 2H), 3.14 (s, 2H), 3.06 (m, 2H), 2.52 (m, 2H), 2.21 (s, 3H), 1.80 (m, 2H) ppm; ES-MS *m/z* 500 (MH<sup>+</sup>).

20

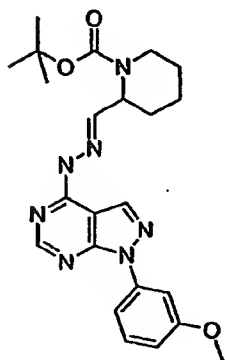


216

Example 128

*tert*-Butyl 2-((*E*)-{[1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazono}methyl)piperidine-1-carboxylate

5

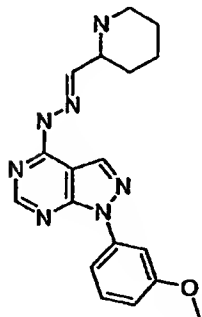


10 A mixture of 4-hydrazino-1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (Intermediates Example T) (330 mg, 1.29 mmol), *tert*-butyl 2-formylpiperidine-1-carboxylate (550mg, 2.58 mmol) and pyrrolidine (2 drops) in ethanol (25 mL) was heated to 100 °C for 18 h. The reaction was then cooled to RT, and the solid collected by filtration and washed with diethyl ether and ethanol to provide product as a white solid (275 mg, 47% yield).

15

<sup>1</sup>H NMR (400 MHz, DMSO) δ 11.96 (s, 1H), 8.43 (s, 1H), 8.38 (s, 1H), 7.81 (m, 2H), 7.44 (m, 2H), 6.91 (d, 1H), 4.94 (m, 1H), 3.91 (d, 1H), 3.81 (s, 3H), 2.00 (d, 1H), 1.68 (m, 2H), 1.61 (m, 2H), 1.38 (s, 9H), 1.30 (m, 2H) ppm; ES-MS *m/z* 452 (MH<sup>+</sup>).

20

**Example 129****Piperidine-2-carbaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone**

5

A mixture of *tert*-butyl 2-((*E*-{1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone)methyl)piperidine-1-carboxylate (Example 135) (171 mg, 0.379 mmol, 1 equiv) and 20% trifluoroacetic acid in dichloromethane (15 mL) was stirred at RT for 18 h. The reaction mixture was partitioned between dichloromethane and satd. aq. NaHCO<sub>3</sub>. The organic layer was dried (MgSO<sub>4</sub>) and concentrated to provide product as a tan solid (101 mg, 76% yield).

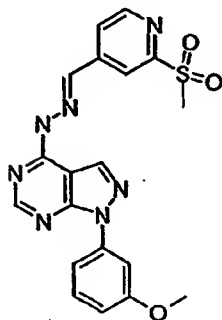
15

<sup>1</sup>H NMR (400 MHz, DMSO) δ 11.88 (s, 1H), 8.48 (s, 1H), 8.42 (s, 1H), 7.81 (m, 2H), 7.49 (d, 1H), 7.44 (t, 1H), 6.91 (d, 1H), 6.81 (d, 1H), 3.81 (s, 3H), 3.36 (m, 1H), 2.96 (m, 1H), 2.58 (t, 1H), 1.78 (m, 2H), 1.46 (m, 4H) ppm; ES-MS *m/z* 352 (MH<sup>+</sup>).

20

**Example 130**

**2-(Methylsulfonyl)isonicotinaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone hydrochloride**



5

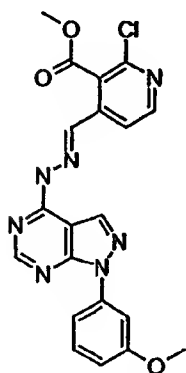
To 4-(diethoxymethyl)-2-(methylsulfonyl)pyridine (Intermediates Example V) (120 mg, 0.46 mmol) in THF (5 mL) was added 4-hydrazino-1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (Intermediates Example T) (90 mg, 0.35 mmol) and 1N aqueous hydrochloric acid (5 mL). The mixture was heated in a 90 °C oil bath for ca. 1.75 h. After cooling to RT the resulting solid was collected by filtration and washed with ether to give the HCl salt of the product as a white solid (93 mg, 57%).

<sup>1</sup>H NMR (DMSO) δ 8.86 (d, 1H), 8.64 (s, 1H), 8.58 (s, 1H), 8.42 (brs, 1H), 8.34 (brs, 1H), 8.16 (d, 1H), 7.84 (m, 2H), 7.48 (t, 1H), 6.96 (d, 1H), 5.11 (brs, 2H), 3.84 (s, 3H), 3.34 (s, 3H) ppm; ES-MS m/z 424 (MH<sup>+</sup>).

15

**Example 131**

**Methyl 2-chloro-4-((E)-{ [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl}hydrazono} methyl)nicotinate hydrochloride**



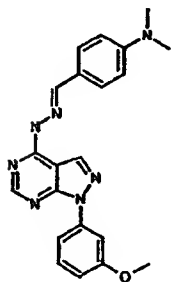
5

To methyl 2-chloro-4-(diethoxymethyl)nicotinate (95 mg, 0.35 mmol) in THF (5 mL) was added 4-hydrazino-1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (Intermediates Example T) (80 mg, 0.31 mmol) and 1N aqueous hydrochloric acid (5 mL). The mixture was heated in a 90 C oil bath for ca. 3.5 h. After cooling to RT the resulting solid was collected by filtration and washed with ether to give the HCl salt of the product as a white solid (60 mg, 41%).

15 <sup>1</sup>H NMR (DMSO) δ 8.66 (s, 1H), 8.59 (m, 2H), 8.30 (s, 1H), 8.12 (d, 1H), 7.85 (m, 2H), 7.48 (t, 1H), 6.96 (dd, 1H), 4.91 (brs, 2H), 3.93 (s, 3H), 3.84 (s, 3H) ppm; ES-MS *m/z* 438 (MH<sup>+</sup>).

20

220

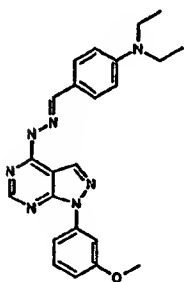
Example 1324-(Dimethylamino)benzaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone

5

A mixture of 4-Hydrazino-1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (Intermediates Example T) (107 mg, 0.417 mmol), 4-(dimethylamino)benzaldehyde (76 mg, 0.511 mmol), and pyrrolidine (2 drops) in EtOH (10 mL) was heated at reflux for 12 h. The solid was filtered and washed with hexanes to yield product (130 mg, 81%) as a yellow solid.

<sup>1</sup>H NMR (400 MHz, DMSO) δ 12.01 (s, 1H), 8.60 (s, 1H), 8.42 (s, 1H), 8.16 (s, 1H), 7.87–7.85 (m, 2H), 7.62 (d, 2H), 7.45 (t, 1H), 6.92 (m, 1H), 6.79 (d, 2H), 3.82 (s, 3H), 2.98 (s, 6H) ppm; ES-MS *m/z* 388 (MH<sup>+</sup>).

20

**Example 133****4-(Diethylamino)benzaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone**

5

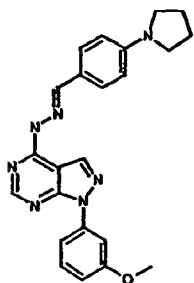
A mixture of 4-Hydrazino-1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (Intermediates Example T) (106 mg, 0.414 mmol), 4-(diethylamino)benzaldehyde (93 mg, 0.525 mmol), and pyrrolidine (2 drops) in EtOH (10 mL) was heated at reflux for 12 h. The solid was filtered and washed with hexanes to yield product (140 mg, 82%) as a yellow solid.

<sup>1</sup>H NMR (400 MHz, DMSO) δ 11.97 (s, 1H), 8.60 (s, 1H), 8.41 (s, 1H), 8.13 (s, 1H), 7.86-7.85 (d+s, 2H), 7.59 (d, 2H), 7.45 (t, 1H), 6.92 (m, 1H), 6.74 (d, 2H), 3.82 (s, 3H), 3.39 (q, 4H), 1.11 (t, 6H) ppm; ES-MS m/z 416 (MH<sup>+</sup>).

20

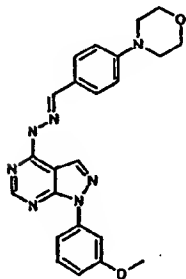
**Example 134**

**4-Pyrrolidin-1-ylbenzaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone**



5

- A mixture of 4-Hydrazino-1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (Intermediates Example T) (100 mg, 0.391 mmol), 4-(1-pyrrolidinyl)benzaldehyde (85 mg, 0.486 mmol), and pyrrolidine (2 drops) in EtOH (10 mL) was heated at reflux for 12 h. The solid was filtered and washed with hexanes to yield product (120 mg, 75%) as a yellow solid.
- <sup>1</sup>H NMR (400 MHz, DMSO) δ 11.97 (s, 1H), 8.60 (s, 1H), 8.41 (s, 1H), 8.14 (s, 1H), 7.87–7.85 (m, 2H), 7.61 (d, 2H), 7.45 (t, 1H), 6.92 (m, 1H), 6.62 (d, 2H), 3.82 (s, 3H), 3.29–3.27 (m, 4H), 1.97–1.94 (m, 4H) ppm; ES-MS *m/z* 414 (MH<sup>+</sup>).
- 10
- 15

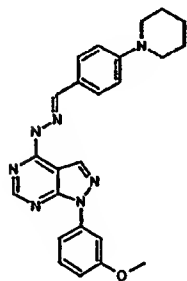
**Example 135****4-Morpholin-4-ylbenzaldehyde [1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone**

5

- A mixture of 4-Hydrazino-1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine (Intermediates Example T) (105 mg, 0.410 mmol), 4-(4-morpholinyl)benzaldehyde (105 mg, 0.549), and pyrrolidine (2 drops) in EtOH (10 mL) was heated at reflux for 12 h. The solid was filtered and washed with hexanes to yield product (137 mg, 76%) as a yellow solid.
- <sup>1</sup>H NMR (400 MHz, DMSO)  $\delta$  12.07 (s, 1H), 8.60 (s, 1H), 8.43 (s, 1H), 8.18 (s, 1H), 7.86-7.84 (m, 2H), 7.66 (d, 2H), 7.45 (t, 1H), 7.03 (d, 2H), 6.92 (m, 1H), 3.82 (s, 3H), 3.74-3.72 (m, 4H), 3.22-3.20 (m, 4H) ppm; ES-MS  $m/z$  430 (MH<sup>+</sup>).

20



**Example 136****4-Piperidin-1-ylbenzaldehyde [1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone**

5

A mixture of 4-Hydrazino-1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine  
10 (Intermediates Example T) (117 mg, 0.457 mmol), 4-(1-piperidiny)benzaldehyde (114  
mg, 0.602 mmol), and pyrrolidine (2 drops) in EtOH (10 mL) was heated at reflux for  
12 h. The solid was filtered and washed with hexanes to yield product (195 mg, 98%)  
as a yellow solid.

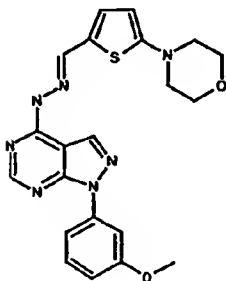
15 <sup>1</sup>H NMR (400 MHz, DMSO) δ 12.03 (s, 1H), 8.59 (s, 1H), 8.42 (s, 1H), 8.16 (s, 1H), 7.86-  
7.84 (d+s, 2H), 7.62 (d, 2H), 7.45 (t, 1H), 6.99 (d, 2H), 6.92 (m, 1H), 3.82 (s, 3H), 3.27 (m,  
4H), 1.57 (m, 6H) ppm; ES-MS m/z 428 (MH<sup>+</sup>).

20

225

**Example 137**

**5-Morpholin-4-ylthiophene-2-carbaldehyde [1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone**



5

A mixture of 4-Hydrazino-1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine (Intermediates Example T) (103 mg, 0.402 mmol), 5-(4-morpholinyl)-2-thiophenecarbaldehyde (96 mg, 0.488 mmol), and pyrrolidine (2 drops) in EtOH (10 mL) was heated at reflux for 12 h. The solid was filtered and washed with hexanes to yield product (162 mg, 95%) as a yellow solid.

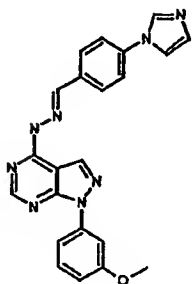
<sup>1</sup>H NMR (400 MHz, DMSO) δ 12.05 (s, 1H), 8.48 (s, 1H), 8.40 (s, 1H), 8.25 (s, 1H), 7.86-7.82 (m, 2H), 7.45 (t, 1H), 7.20 (d, 1H), 6.91 (m, 1H), 6.19 (d, 1H), 3.82 (s, 3H), 3.74-3.72 (m, 4H), 3.23-3.21 (m, 4H) ppm; ES-MS m/z 436 (MH<sup>+</sup>).

20

**Example 138**

**4-(1*H*-imidazol-1-yl)benzaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone**

5



- 10 A mixture of 4-Hydrazino-1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (Intermediates Example T) (106 mg, 0.415 mmol), 4-(1*H*-imidazol-1-yl)benzaldehyde (86 mg, 0.501 mmol), and pyrrolidine (2 drops) in EtOH (10 mL) was heated at reflux for 12 h. The solid was filtered and washed with hexanes to yield product (148 mg, 87%) as a yellow solid.

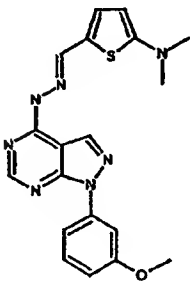
15

<sup>1</sup>H NMR (400 MHz, DMSO)  $\delta$  12.31 (s, 1H), 8.64 (s, 1H), 8.48 (s, 1H), 8.34 (s, 1H), 8.31 (s, 1H), 7.94 (d, 2H), 7.86-7.82 (m, 3H), 7.76 (d, 2H), 7.45 (t, 1H), 7.13 (s, 1H), 6.92 (m, 1H), 3.82 (s, 3H) ppm; ES-MS  $m/z$  411 (MH<sup>+</sup>).

20

**Example 139**

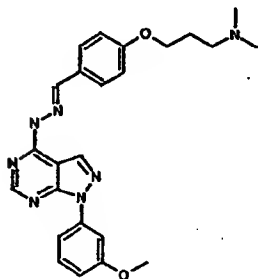
**5-(Dimethylamino)thiophene-2-carbaldehyde [1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone**



5

- A mixture of 4-Hydrazino-1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine (Intermediates Example T) (100 mg, 0.392 mmol), 5-(dimethylamino)-2-thiophenecarbaldehyde (77 mg, 0.499 mmol), and pyrrolidine (2 drops) in EtOH (10 mL) was heated at reflux for 12 h. The solid was filtered and washed with hexanes to yield product (142 mg, 95%) as a yellow solid.
- <sup>1</sup>H NMR (400 MHz, DMSO) δ 11.97 (s, 1H), 8.48 (s, 1H), 8.38 (s, 1H), 8.22 (s, 1H), 7.87–7.83 (m, 2H), 7.44 (t, 1H), 7.16 (d, 1H), 6.91 (m, 1H), 5.90 (d, 1H), 3.82 (s, 3H), 3.00 (s, 6H) ppm; ES-MS m/z 394 (MH<sup>+</sup>).

20

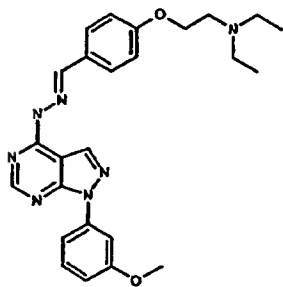
Example 1404-[3-(Dimethylamino)propoxy]benzaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone

5

A mixture of 4-Hydrazino-1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine

- 10 (Intermediates Example T) (110 mg, 0.428 mmol), 4-[3-(dimethylamino)propoxy]benzaldehyde (0.105 mL, 0.522 mmol), and pyrrolidine (2 drops) in EtOH (10 mL) was heated at reflux for 12 h. The solid was filtered and washed with hexanes to yield product (170 mg, 89%) as a yellow solid.

- 15 <sup>1</sup>H NMR (400 MHz, DMSO) δ 12.11 (s, 1H), 8.61 (s, 1H), 8.45 (s, 1H), 8.22 (s, 1H), 7.86-7.83 (m, 2H), 7.74 (d, 2H), 7.45 (t, 1H), 7.02 (d, 2H), 6.92 (m, 1H), 4.04 (t, 2H), 3.82 (s, 3H), 2.35 (t, 2H), 2.13 (s, 6H), 1.84 (m, 2H) ppm; ES-MS *m/z* 446 (MH<sup>+</sup>).

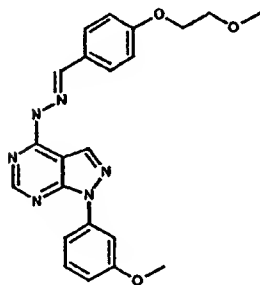
**Example 141****4-[2-(Diethylamino)ethoxy]benzaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone**

5

- A mixture of 4-Hydrazino-1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (Intermediates Example T) (106 mg, 0.412 mmol), 4-[2-(diethylamino)ethoxy]benzaldehyde (132 mg, 0.595 mmol), and pyrrolidine (2 drops) in EtOH (10 mL) was heated at reflux for 12 h. The solid was filtered and washed with hexanes to yield product (90 mg, 48%) as a yellow solid.
- <sup>1</sup>H NMR (400 MHz, DMSO): δ 12.13 (s, 1H), 8.61 (s, 1H), 8.45 (s, 1H), 8.23 (s, 1H), 7.87-7.84 (m, 2H), 7.74 (d, 2H), 7.46 (t, 1H), 7.03 (d, 2H), 6.92 (m, 1H), 4.06 (t, 2H), 3.82 (s, 3H), 2.78 (m, 2H), 2.53 (m, 4H), 0.96 (t, 6H) ppm; ES-MS *m/z* 460 (MH<sup>+</sup>).
- 10
- 15

**Example 142**

**4-(2-Methoxyethoxy)benzaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone**



5

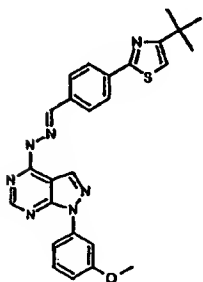
A mixture of 4-Hydrazino-1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine

- 10 (Intermediates Example T) (104 mg, 0.405 mmol), 4-(2-methoxyethoxy)benzaldehyde (109 mg, 0.607 mmol), and pyrrolidine (2 drops) in EtOH (10 mL) was heated at reflux for 12 h. The solid was filtered and washed with hexanes to yield product (114 mg, 67%) as an off-white solid.

- 15 <sup>1</sup>H NMR (400 MHz, DMSO): δ 12.15 (s, 1H), 8.62 (s, 1H), 8.46 (s, 1H), 8.23 (s, 1H), 7.87-7.84 (m, 2H), 7.76 (d, 2H), 7.46 (t, 1H), 7.05 (d, 2H), 6.92 (m, 1H), 4.15 (t, 2H), 3.83 (s, 3H), 3.67 (t, 2H), 3.30 (s, 3H) ppm; ES-MS m/z 419 (MH<sup>+</sup>).

Example 1434-(4-*tert*-Butyl-1,3-thiazol-2-yl)benzaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone

5



- 10 A mixture of 4-Hydrazino-1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (Intermediates Example T) (108 mg, 0.423 mmol), 4-(4-*tert*-butyl-1,3-thiazol-2-yl)benzaldehyde (131 mg, 0.533 mmol), and pyrrolidine (2 drops) in EtOH (10 mL) was heated at reflux for 12 h. The solid was filtered and washed with hexanes to yield product (164 mg, 82%) as a yellow solid.

15

<sup>1</sup>H NMR (400 MHz, DMSO)  $\delta$  12.35 (s, 1H), 8.67 (s, 1H), 8.50 (s, 1H), 8.32 (s, 1H), 8.03 (d, 2H), 7.93 (d, 2H), 7.87-7.84 (m, 2H), 7.47 (t, 1H), 7.37 (s, 1H), 6.93 (m, 1H), 3.83 (s, 3H), 1.35 (s, 9H) ppm; ES-MS *m/z* 484 (MH<sup>+</sup>).

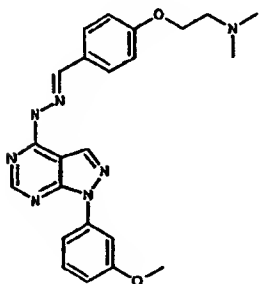
20



Example 144

4-[2-(Dimethylamino)ethoxy]benzaldehyde [1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone

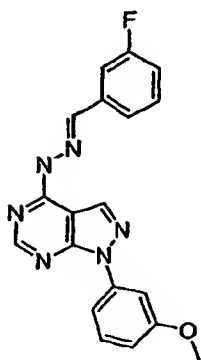
5



- 10 A mixture of 4-Hydrazino-1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine (Intermediates Example T) (98 mg, 0.384 mmol), 4-[2-(dimethylamino)ethoxy]benzaldehyde (Intermediates Example GG) (200 mg, 1.035 mmol), and pyrrolidine (2 drops) in EtOH (10 mL) was heated at reflux for 12 h. The solid was filtered and washed with hexanes to yield product (114 mg, 67%) as a yellow solid.
- 15

<sup>1</sup>H NMR (400 MHz, DMSO) δ 12.14 (s, 1H), 8.62 (s, 1H), 8.45 (s, 1H), 8.23 (s, 1H), 7.87-7.84 (m, 2H), 7.75 (d, 2H), 7.46 (t, 1H), 7.05 (d, 2H), 6.92 (m, 1H), 4.10 (t, 2H), 3.82 (s, 3H), 2.63 (t, 2H), 2.21 (s, 6H) ppm; ES-MS m/z 432 (MH<sup>+</sup>).

20

Example 1453-Fluorobenzaldehyde [1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone

5

Prepared from 4-hydrazino-1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine

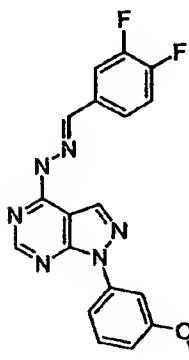
10 (Intermediates Example T) and 3-fluorobenzaldehyde using the general procedure for nicotinaldehyde [1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone (Example 72).

15 <sup>1</sup>H-NMR (400 MHz, DMSO) δ 12.35 (s, 1H), 8.64 (s, 1H), 8.50 (s, 1H), 8.29 (s, 1H), 7.83 (m, 2H), 7.64 (m, 2H), 7.54 (m, 1H), 7.46 (t, 1H), 7.27 (dt, 1H), 6.93 (dd, 1H), 3.82 (s, 3H) ppm; ES-MS m/z 363 (MH<sup>+</sup>).

Example 146

3,4-Difluorobenzaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone

5



- 10 Prepared from 4-hydrazino-1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (Intermediates Example T) and 3,4-difluorobenzaldehyde using the general procedure for nicotinaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone (Example 72).

- 15 <sup>1</sup>H NMR (400 MHz, DMSO) δ 12.27 (s, 1H), 8.65 (s, 1H), 8.49 (s, 1H), 8.25 (s, 1H), 7.85 (m, 3H), 7.69 (m, 1H), 7.53 (m, 1H), 7.46 (t, 1H), 6.93 (dd, 1H), 3.82 (s, 3H) ppm; ES-MS *m/z* 381 (MH<sup>+</sup>).

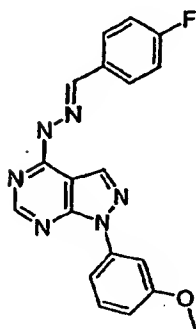
20

235

Example 147

4-Fluorobenzaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone

5



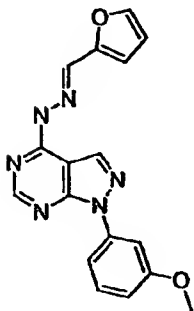
10

Prepared from 4-hydrazino-1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (Intermediates Example T) and 4-fluorobenzaldehyde using the general procedure for nicotinaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone (Example 72).

15

<sup>1</sup>H NMR (400 MHz, DMSO) δ 12.35 (s, 1H), 8.63 (s, 1H), 8.48 (s, 1H), 8.28 (s, 1H), 7.86 (m, 4H), 7.45 (t, 1H), 7.31 (t, 2H), 6.93 (dd, 1H), 3.82 (s, 3H) ppm; ES-MS *m/z* 363 (MH<sup>+</sup>).

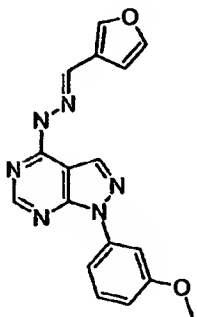
20

**Example 148****2-Furaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone**

5

Prepared from 4-hydrazino-1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine  
 10 (Intermediates Example T) and 2-furaldehyde using the general procedure for  
 nicotinaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone  
 (Example 72).

<sup>1</sup>H NMR (400 MHz, DMSO) δ 12.21 (s, 1H), 8.60 (s, 1H), 8.46 (s, 1H), 8.15 (s, 1H), 7.84 (m,  
 15 3H), 7.45 (t, 1H), 7.03 (d, 1H), 6.92 (d, 1H), 6.66 (m, 1H), 3.82 (s, 3H) ppm; ES-MS *m/z*  
 335 (MH<sup>+</sup>).

**Example 149****3-Furaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone**

5

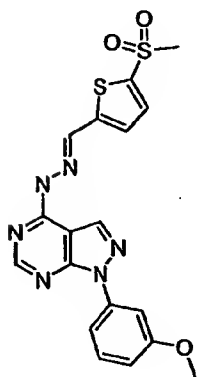
Prepared from 4-hydrazino-1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine  
(Intermediates Example T) and 3-furaldehyde using the general procedure for  
10 nicotinaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone  
(Example 72).

<sup>1</sup>H NMR (400 MHz, DMSO) δ 12.14 (s, 1H), 8.62 (s, 1H), 8.45 (s, 1H), 8.23 (m, 2H), 7.83  
(m, 3H), 7.46 (t, 1H), 7.08 (s, 1H), 6.92 (dd, 1H), 3.82 (s, 3H) ppm; ES-MS *m/z* 335 (MH<sup>+</sup>).

**Example 150**

**5-(Methylsulfonyl)thiophene-2-carbaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone**

5



10

Prepared from 4-hydrazino-1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (Intermediates Example T) and 5-(methylsulfonyl)thiophene-2-carbaldehyde using the general procedure for nicotinaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone (Example 72).

15

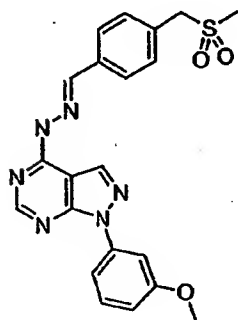
<sup>1</sup>H NMR (400 MHz, DMSO) δ 12.60 (s, 1H), 8.83 (s, 2H), 8.48 (s, 1H), 7.83 (m, 2H), 7.79 (d, 1H), 7.62 (d, 1H), 7.47 (t, 1H), 6.94 (dd, 1H), 3.82 (s, 3H), 3.42 (s, 3H) ppm; ES-MS *m/z* 335 (MH<sup>+</sup>).

20

**Example 151**

**4-[[[(Methylsulfonyl)methyl]benzaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]]hydrazone**

5



- 10 Prepared from 4-hydrazino-1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (Intermediates Example T) and 4-[(methylsulfonyl)methyl]benzaldehyde (Intermediates Example HH) using the general procedure for nicotinaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone (Example 72).

15 <sup>1</sup>H NMR (400 MHz, DMSO) δ 12.29 (s, 1H), 8.67 (s, 1H), 8.50 (s, 1H), 8.31 (s, 1H), 7.86 (m, 4H), 7.53 (m, 2H), 7.47 (t, 1H), 6.94 (dd, 1H), 4.56 (s, 2H), 3.82 (s, 3H), 2.93 (s, 3H) ppm; ES-MS *m/z* 437 (MH<sup>+</sup>).

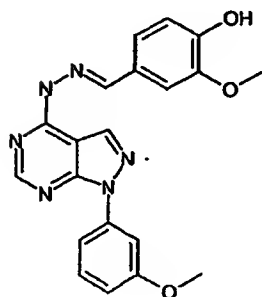
20



240

Example 1524-Hydroxy-3-methoxybenzaldehyde [1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone

5



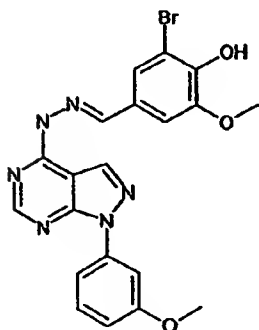
- 10 Prepared from 4-hydrazino-1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine (Intermediates Example T) and 4-Hydroxy-3-methoxybenzaldehyde using the general procedure for nicotinaldehyde [1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone (Example 72).

- 15 <sup>1</sup>H NMR (400 MHz, DMSO) δ 12.08 (s, 1H), 9.59 (s, 1H), 8.57 (s, 1H), 8.43 (s, 1H), 8.16 (s, 1H), 7.82 (m, 2H), 7.43 (t, 1H), 7.32 (s, 1H), 7.20 (d, 1H), 6.85-6.91 (m, 2H), 3.86 (s, 3H), 3.81 (s, 3H) ppm ES-MS m/z 391 (MH<sup>+</sup>).

20

**Example 153**

**3-Bromo-4-hydroxy-5-methoxybenzaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone**



5

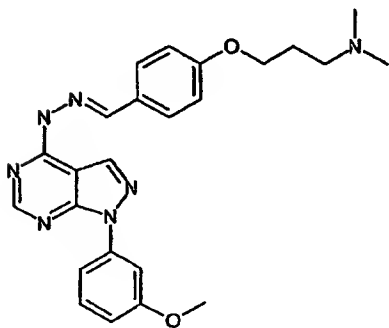
Prepared from 4-hydrazino-1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine  
 10 (Intermediates Example T) and 3-Bromo-4-hydroxy-5-methoxybenzaldehyde using  
 the general procedure for nicotinaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]  
 pyrimidin-4-yl]hydrazone (Example 72).

<sup>1</sup>H NMR (400 MHz, DMSO) δ 8.52 (s, 1H), 8.39 (s, 1H), 8.06 (s, 1H), 7.82-7.86 (m, 2H),  
 15 7.43 (t, 1H), 7.32 (s, 1H), 7.20 (s, 1H), 6.90 (m, 1H), 3.83 (s, 3H), 3.81 (s, 3H) ppm; ES-MS  
 m/z 470 (MH<sup>+</sup>).

Example 154

4-[3-(Dimethylamino)propoxy]benzaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone

5

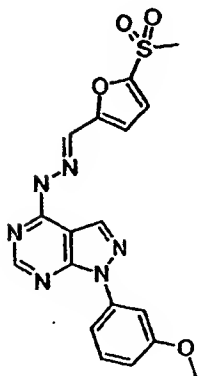


- 10 Prepared from 4-hydrazino-1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (Intermediates Example T) and 4-[3-(Dimethylamino)propoxy]benzaldehyde using the general procedure for nicotinaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone (Example 72).
- 15 <sup>1</sup>H NMR (400 MHz, DMSO) δ 12.17 (s, 1H), 8.61 (s, 1H); 8.44 (s, 1H), 8.24 (s, 1H), 7.82 (m, 2H), 7.76 (d, 2H), 7.44 (m, 1H), 7.04 (d, 2H), 6.91 (m, 1H), 4.10 (m, 2H), 3.81 (s, 3H), 3.19 (m, 2H), 2.75 (s, 6H), 2.14 (m, 2H) ppm; ES-MS *m/z* 483 (MH<sup>+</sup>).

Example 155

5-(methylsulfonyl)-2-furaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone

5



Prepared from 4-hydrazino-1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine

- 10 (Intermediates Example T) using the general procedure for isonicotinaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone (Example 73).

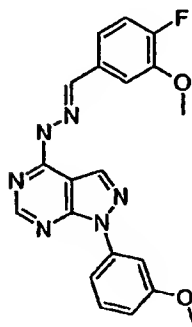
<sup>1</sup>H NMR (400 MHz, DMSO) δ 12.51 (s, 1H), 8.60 (s, 1H), 8.52 (s, 1H), 8.21 (s, 1H), 7.84 (m, 2H), 7.45 (t, 1H), 7.42 (d, 1H), 7.27 (d, 1H), 6.93 (d, 1H), 3.82 (s, 3H), 3.39 (s, 3H). ES-

- 15 MS m/z 412 (MH<sup>+</sup>).

**Example 156**

**4-fluoro-3-methoxybenzaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone**

5

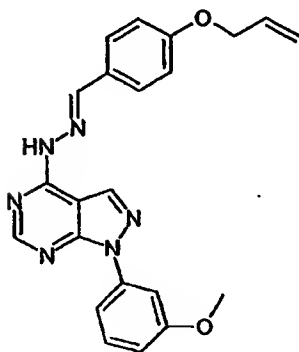


Prepared from 4-hydrazino-1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine

- 10 (Intermediates Example T) using the general procedure for isonicotinaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone (Example 73).

<sup>1</sup>H NMR (400 MHz, DMSO) δ 12.32 (s, 1H), 8.61 (s, 1H), 8.49 (s, 1H), 8.26 (s, 1H), 7.85 (m, 2H), 7.54 (d, 1H), 7.46 (t, 1H), 7.41 (m, 1H), 7.32 (dd, 1H), 6.93 (dd, 1H), 3.95 (s, 3H),

15 3.83 (s, 3H). ES-MS *m/z* 392 (MH<sup>+</sup>).

**Example 157****4-(Allyloxy)benzaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone**

5

Prepared from 4-hydrazino-1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (Intermediates Example T) and 4-(allyloxy)benzaldehyde using the general procedure for isonicotinaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone (Example 73).

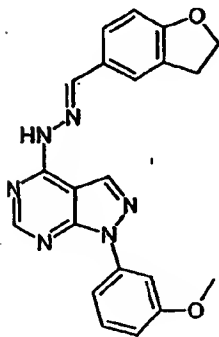
10

<sup>1</sup>H NMR (400 MHz, DMSO): δ 12.14 (s, 1H), 8.62 (s, 1H), 8.46 (s, 1H), 8.23 (s, 1H), 7.87 (m, 1H), 7.86-7.84 (m, 1H), 7.76 (d, 2H, J = 8.8), 7.46 (t, 1H, J = 8.2), 7.06 (d, 2H, J = 8.8), 6.94-6.91 (m, 1H), 6.05 (m, 1H), 5.41 (m, 1H), 5.27 (m, 1H), 4.63 (m, 2H), 3.83 (s, 3H). ES-MS m/z 401 (MH<sup>+</sup>).

15

**Example 158**

**2,3-Dihydro-1-benzofuran-5-carbaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone**



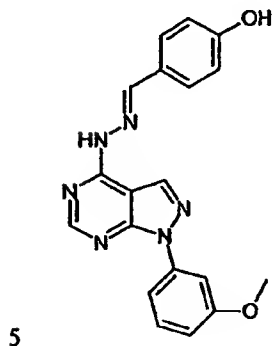
Prepared from 4-hydrazino-1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (Intermediates Example T) and 2,3-dihydro-1-benzofuran-5-carbaldehyde using the general procedure for isonicotinaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone (Example 73).

10

<sup>1</sup>H NMR (400 MHz, DMSO): δ 12.07 (s, 1H), 8.63 (s, 1H), 8.44 (s, 1H), 8.21 (s, 1H), 7.87 (m, 1H), 7.85-7.83 (m, 1H), 7.77 (m, 1H), 7.49-7.43 (m, 2H), 6.93-6.90 (m, 1H), 6.84 (d, 1H, J = 8.3), 4.59 (t, 2H, J = 8.7), 3.82 (s, 3H), 3.28-3.23 (m, 2H). ES-MS m/z 396 (MH<sup>+</sup>).

**Example 159**

**4-Hydroxybenzaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone**



Prepared from 4-hydrazino-1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (Intermediates Example T) and 4-formylphenyl phenylcarbamate using the general procedure for isonicotinaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone (Example 73).

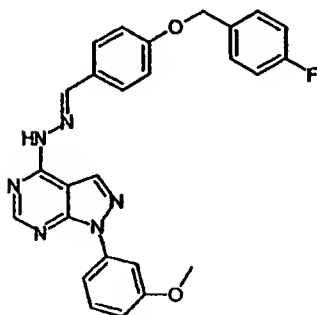
10

<sup>1</sup>H NMR (400 MHz, DMSO): δ 12.06 (s, 1H), 9.95 (s, 1H), 8.61 (s, 1H), 8.44 (s, 1H), 8.19 (s, 1H), 7.87-7.84 (m, 2H), 7.65 (d, 2H, J = 8.6), 7.45 (t, 1H, J = 8.0), 6.93-6.91 (m, 1H), 6.87 (d, 2H, J = 8.6), 3.82 (s, 3H). ES-MS m/z 361 (MH<sup>+</sup>).



Example 160

4-[(4-Fluorobenzyl)oxy]benzaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone



5

Prepared from 4-hydrazino-1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (Intermediates Example T) and 4-[(4-fluorobenzyl)oxy]benzaldehyde using the general procedure for isonicotinaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone (Example 73).

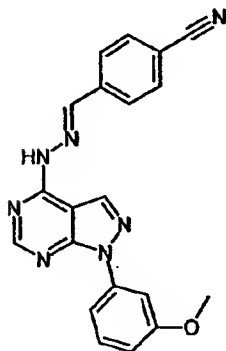
10

<sup>1</sup>H NMR (400 MHz, DMSO): δ 12.15 (s, 1H), 8.63 (s, 1H), 8.46 (s, 1H), 8.24 (s, 1H), 7.87-7.84 (m+m, 2H), 7.77 (d, 2H, J = 8.8), 7.54-7.50 (m, 2H), 7.46 (t, 1H, J = 8.2), 7.25-7.20 (m, 2H), 7.12 (d, 2H, J = 8.6), 6.94-6.91 (m, 1H), 5.15 (s, 2H), 3.83 (s, 3H). ES-MS m/z 469 (MH<sup>+</sup>).

----- 15

## Example 161

4-((E)-{[1-(3-Methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazono} methyl)benzonitrile



5

Prepared from 4-hydrazino-1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine

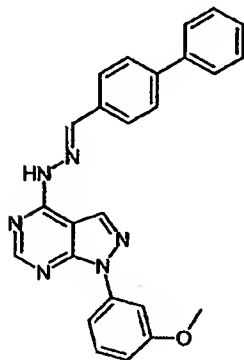
- 10 (Intermediates Example T) and 4-formylbenzonitrile using the general procedure for isonicotinaldehyde [1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone (Example 73).

- 15 <sup>1</sup>H NMR (400 MHz, DMSO): δ 12.48 (s, 1H), 8.66 (s, 1H), 8.53 (s, 1H), 8.32 (s, 1H), 8.01 (d, 2H, J = 8.4), 7.92 (d, 2H, J = 8.5), 7.87-7.82 (m+m, 2H), 7.47 (t, 1H, J = 8.2), 6.95-6.92 (m, 1H), 3.83 (s, 3H). ES-MS m/z 370 (MH<sup>+</sup>).

250

**Example 162**

1,1'-Biphenyl-4-carbaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone



5

Prepared from 4-hydrazino-1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (Intermediates Example T) and 1,1'-biphenyl-4-carbaldehyde using the general procedure for isonicotininaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone (Example 73).

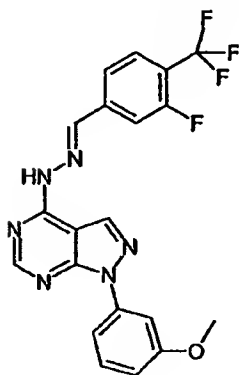
10

<sup>1</sup>H NMR (400 MHz, DMSO): δ 12.31 (s, 1H), 8.68 (s, 1H), 8.50 (s, 1H), 8.34 (s, 1H), 7.91 (d, 2H, *J* = 8.5), 7.88–7.85 (m, 2H), 7.80 (d, 2H, *J* = 8.3), 7.73 (m, 2H), 7.51–7.45 (m, 3H), 7.39 (t, 1H, *J* = 7.3), 6.95–6.93 (m, 1H), 3.83 (s, 3H). ES-MS *m/z* 421 (MH<sup>+</sup>).

15

**Example 163**

**3-Fluoro-4-(trifluoromethyl)benzaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone**



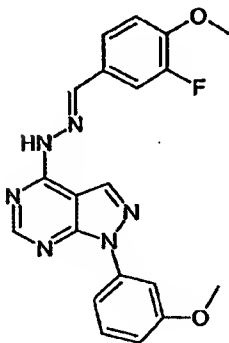
5

Prepared from 4-hydrazino-1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (Intermediates Example T) and 3-fluoro-4-(trifluoromethyl)benzaldehyde using the general procedure for isonicotinaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone (Example 73).

10

<sup>1</sup>H NMR (400 MHz, DMSO): δ 12.49 (s, 1H), 8.65 (s, 1H), 8.52 (s, 1H), 8.31 (s, 1H), 7.90-7.81 (m, 5H), 7.45 (t, 1H, J = 8.2), 6.94-6.91 (m, 1H), 3.82 (s, 3H). ES-MS m/z 431 (MH<sup>+</sup>).

15

Example 1643-Fluoro-4-methoxybenzaldehyde [1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone

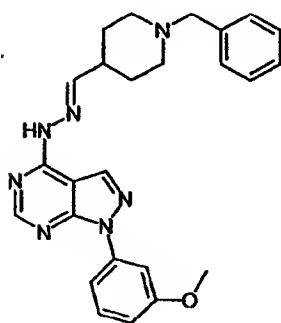
5

Prepared from 4-hydrazino-1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine (Intermediates Example T) and 3-fluoro-4-methoxybenzaldehyde using the general  
10 procedure for isonicotinaldehyde [1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone (Example 73).

<sup>1</sup>H NMR (400 MHz, DMSO): δ 12.21 (s, 1H), 8.63 (s, 1H), 8.47 (s, 1H), 8.22 (s, 1H), 7.86-  
7.83 (m, 2H), 7.70-7.67 (m, 1H), 7.58-7.57 (m, 1H), 7.46 (t, 1H, J = 8.1), 7.26 (t, 1H, J =  
15 8.6), 6.94-6.91 (m, 1H), 3.89 (s, 3H), 3.82 (s, 3H). ES-MS m/z 393 (MH<sup>+</sup>).

**Example 165****1-Benzylpiperidine-4-carbaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone**

5

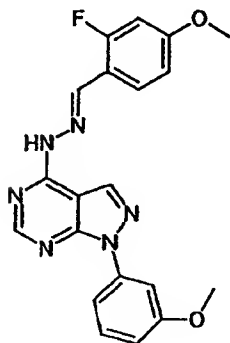


- Prepared from 4-hydrazino-1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine  
 10 (Intermediates Example T) and 1-benzylpiperidine-4-carbaldehyde using the general  
 procedure for isonicotinaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-  
 4-yl]hydrazone (Example 73).

<sup>1</sup>H NMR (400 MHz, DMSO): δ 11.80 (s, 1H), 8.41 (s, 2H), 7.84-7.80 (m, 2H), 7.58 (d, 1H,  
 15  $J = 4.1$ ), 7.44 (t, 1H;  $J = 8.1$ ), 7.33-7.28 (m; 4H), 7.25-7.19 (m, 1H), 6.92-6.90 (m, 1H),  
 3.81 (s, 3H), 3.46 (s, 2H), 2.86-2.84 (m, 2H), 2.41-2.32 (m, 1H), 2.03 (m, 2H), 1.89-1.85  
 (m, 2H), 1.57-1.48 (m, 2H). ES-MS *m/z* 442 (MH<sup>+</sup>).

**Example 166**

**2-Fluoro-4-methoxybenzaldehyde [1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone**



5

Prepared from 4-hydrazino-1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine (Intermediates Example T) and 2-fluoro-4-methoxybenzaldehyde using the general procedure for isonicotinaldehyde [1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone (Example 73).

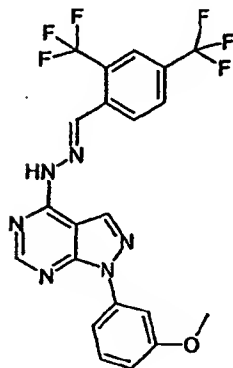
<sup>1</sup>H NMR (400 MHz, DMSO): δ 12.18 (s, 1H), 8.61 (s, 1H), 8.46 (s, 1H), 8.39 (s, 1H), 7.97 (m, 1H), 7.86-7.82 (m, 2H), 7.45 (t, 1H, J = 8.1), 6.96-6.91 (m, 3H), 3.82 (s, 6H). ES-MS m/z 393 (MH<sup>+</sup>).

15

255

Example 167

2,4-Bis(trifluoromethyl)benzaldehyde [1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone



5

Prepared from 4-hydrazino-1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine (Intermediates Example T) and 2,4-bis(trifluoromethyl)benzaldehyde using the general procedure for isonicotinaldehyde [1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone (Example 73).

<sup>1</sup>H NMR (400 MHz, DMSO): δ 12.61 (s, 1H), 8.65 (s, 1H), 8.63 (s, 1H), 8.58-8.54 (m, 2H), 8.15 (d, 1H, J = 7.4), 8.08 (s, 1H), 7.84-7.81 (m, 2H), 7.45 (t, 1H, J = 7.9), 6.94-6.91 (m, 1H), 3.81 (s, 3H). ES-MS m/z 481 (MH<sup>+</sup>).

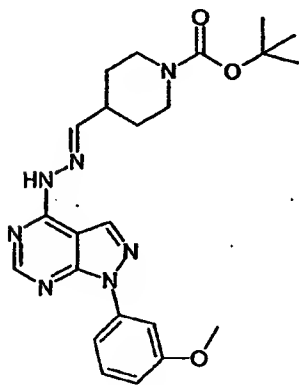
15



256

Example 168

tert-Butyl 4-((E)-{[1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazono}methyl)piperidine-1-carboxylate

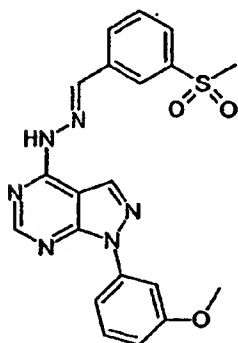


5

Prepared from 4-hydrazino-1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine (Intermediates Example T) and tert-butyl 4-formylpiperidine-1-carboxylate using the  
 10 general procedure for isonicotinaldehyde [1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone (Example 73).

<sup>1</sup>H NMR (400 MHz, DMSO): δ 11.83 (s, 1H), 8.41 (s, 2H), 7.83-7.81 (m, 2H), 7.57 (m, 1H), 7.44 (t, 1H, J = 8.0), 6.91 (m, 1H), 3.97 (m, 2H), 3.81 (s, 3H), 2.84 (m, 2H), 2.56 (m, 1H), 1.89 (m, 2H), 1.38 (s+m, 10H). ES-MS m/z 452 (MH<sup>+</sup>).

15

Example 1693-(Methylsulfonyl)benzaldehyde [1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone

5

Prepared from 4-hydrazino-1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine (Intermediates Example T) and 3-(methylsulfonyl)benzaldehyde using the general procedure for isonicotinaldehyde [1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone (Example 73).

10

<sup>1</sup>H NMR (400 MHz, DMSO): δ 12.46 (s, 1H), 8.64 (s, 1H), 8.52 (s, 1H), 8.40 (s, 1H), 8.27 (m, 1H), 8.22 (d, 1H, J = 8.1), 7.99-7.97 (m, 1H), 7.88-7.86 (m, 1H), 7.84 (m, 1H), 7.77 (t, 1H, J = 7.8), 7.45 (t, 1H, J = 8.2), 6.95-6.93 (m, 1H), 3.83 (s, 3H), 3.30 (s, 3H). ES-MS m/z 423 (MH<sup>+</sup>).

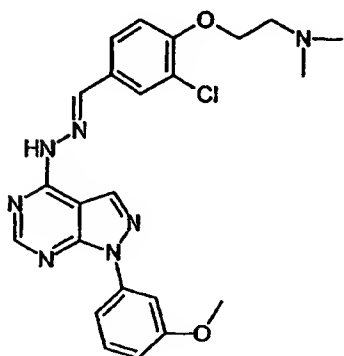
15

258

**Example 170**

**3-Chloro-4-[2-(dimethylamino)ethoxy]benzaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone**

5



Prepared from 4-hydrazino-1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (Intermediates Example T) and 3-chloro-4-[2-(dimethylamino)ethoxy]benzaldehyde using the general procedure for isonicotinaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone (Example 73).

10

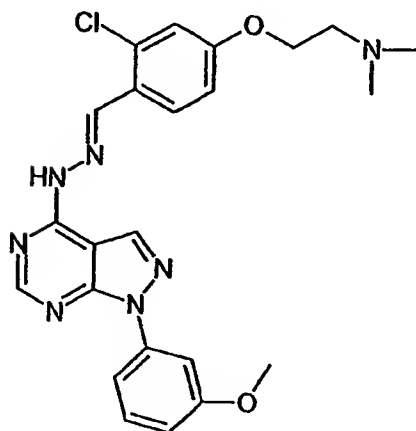
<sup>1</sup>H NMR (400 MHz, DMSO): δ 12.20 (s, 1H), 8.58 (s, 1H), 8.46 (s, 1H), 8.20 (s, 1H), 7.86-7.82 (m, 3H), 7.76-7.74 (m, 1H), 7.45 (t, 1H, J = 8.1), 7.26 (d, 1H, J = 8.6), 6.93-6.91 (m, 1H), 4.19 (t, 2H, J = 5.7), 3.82 (s, 3H), 2.67 (t, 2H, J = 5.7), 2.23 (s, 6H). ES-MS m/z 466 (MH<sup>+</sup>).

15

20

**Example 171**

**2-Chloro-4-[2-(dimethylamino)ethoxy]benzaldehyde [1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone**



5

Prepared from 4-hydrazino-1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine (Intermediates Example T) and 2-chloro-4-[2-(dimethylamino)ethoxy]benzaldehyde using the general procedure for isonicotinaldehyde [1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone (Example 73).

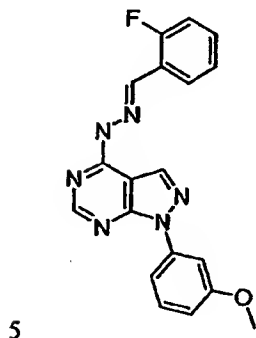
10

<sup>1</sup>H NMR (400 MHz, DMSO): δ 12.27 (s, 1H), 8.60 (s, 1H), 8.59 (s, 1H), 8.47 (s, 1H), 7.86-7.82 (m, 3H), 7.45 (t, 1H, J = 8.1), 7.12 (m, 1H), 7.08-7.05 (m, 1H), 6.93-6.91 (m, 1H), 4.11 (t, 2H, J = 5.7), 3.82 (s, 3H), 2.61 (t, 2H, J = 5.6), 2.19 (s, 6H). ES-MS m/z 466 (MH<sup>+</sup>).

15

Example 172

2-fluorobenzaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone



- Prepared from 4-hydrazino-1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine  
 10 (Intermediates Example T) using the general procedure for isonicotinaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone (Example 73).

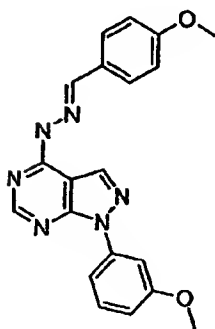
<sup>1</sup>H NMR (400 MHz, DMSO) δ 12.34 (s, 1H), 8.65 (s, 1H), 8.51 (s, 1H), 8.50 (s, 1H), 8.08 (t, 1H), 7.84 (m, 2H), 7.50 (m, 2H), 7.32 (m, 2H), 6.94 (dd, 1H), 3.83 (s, 3H). ES-MS *m/z*

15 363 (MH<sup>+</sup>).

**Example 173**

**4-methoxybenzaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone**

5

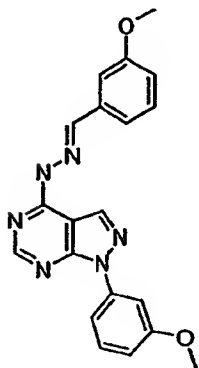


- 10 Prepared from 4-hydrazino-1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (Intermediates Example T) using the general procedure for isonicotinaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone (Example 73).

<sup>1</sup>H NMR (400 MHz, DMSO) δ 12.09 (s, 1H), 8.62 (s, 1H), 8.46 (s, 1H), 8.24 (s, 1H), 7.86 (m, 2H), 7.77 (d, 2H), 7.46 (t, 1H), 7.05 (d, 2H), 6.93 (d, 1H), 3.83 (s, 3H), 3.81 (s, 3H). ES-MS m/z 375 (MH<sup>+</sup>).

**Example 174**

**3-methoxybenzaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone**



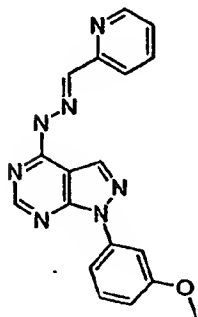
5

- 10 Prepared from 4-hydrazino-1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (Intermediates Example T) using the general procedure for isonicotinaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone (Example 73).

15 <sup>1</sup>H NMR (400 MHz, DMSO) δ 12.26 (s, 1H), 8.59 (s, 1H), 8.49 (s, 1H), 8.27 (s, 1H), 7.84 (m, 2H), 7.46 (t, 1H), 7.41 (m, 2H), 7.31 (s, 1H), 7.02 (m, 1H), 6.93 (m, 1H), 3.84 (s, 3H), 3.83 (s, 3H). ES-MS *m/z* 375 (MH<sup>+</sup>).

**Example 175**

**Pyridine-2-carbaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone**

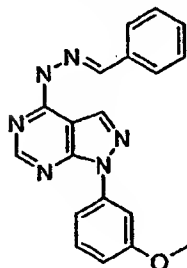


5

- 10 Prepared from 4-hydrazino-1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (Intermediates Example T) using the general procedure for isonicotinaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone (Example 73).

<sup>1</sup>H NMR (400 MHz, DMSO) δ 12.50 (s, 1H), 8.73 (s, 1H), 8.64 (d, 1H), 8.54 (s, 1H), 8.35 (s, 1H), 8.20 (d, 1H), 7.95 (t, 1H), 7.85 (m, 2H), 7.47 (m, 2H), 6.95 (dd, 1H), 3.84 (s, 3H). ES- MS m/z 335 (MH<sup>+</sup>).



**Example 176****Benzaldehyde [1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone**

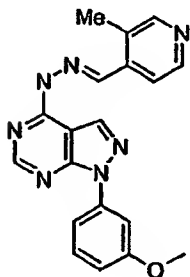
5

Benzaldehyde (46 mg, 0.43 mmol) and pyrrolidine (1 drop) were added to a stirred solution of 4-hydrazino-1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine (Intermediates Example T) (100 mg, 0.39 mmol) in ethanol (5 mL) to give the desired product as a white solid (91 mg, 68%).

10

<sup>1</sup>H NMR (DMSO) δ 12.31 (s, 1H), 8.69 (s, 1H), 8.53 (s, 1H), 8.34 (s, 1H), 7.92-7.86 (m, 4H), 7.57-7.48 (m, 4H), 6.98 (d, 1H), 3.87 (s, 3H) ppm; ES-MS m/z 343 (MH<sup>+</sup>).

15

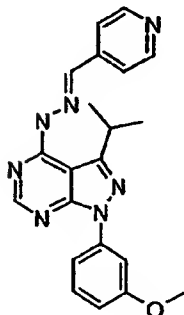
**Example 177****3-methylisonicotinaldehyde [1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone**

5

3-Methylisonicotinaldehyde (52 mg, 0.43 mmol) (Intermediates Example JJ) and pyrrolidine (1 drop) were added to a stirred solution of 4-hydrazino-1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (Intermediates Example T) (100 mg, 0.39 mmol) in ethanol (5 mL) to give the desired product as a white solid (119 mg, 85%).

<sup>1</sup>H NMR (DMSO) δ 12.37 (s, 1H), 8.61 (s, 1H), 8.51-8.48 (m, 4H), 7.87-7.81 (m, 3H), 7.45 (t, 1H), 6.91 (d, 1H), 3.81 (s, 3H), 2.40 (s, 3H) ppm; ES-MS *m/z* 358 (MH<sup>+</sup>).

15

**Example 178****Isonicotinaldehyde [3-isopropyl-1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone**

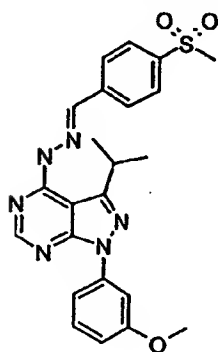
5

To a stirred solution of 4-hydrazino-3-isopropyl-1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine (Intermediates Example LL) (100 mg, 0.335 mmol) in ethanol (3 ml) was added isonicotinaldehyde (47 mL, 0.499 mmol) and pyrrolidine. The resulting mixture was refluxed for ca. 3 hours, cooled to RT, and filtered to give the product as a white solid (94.1 mg, 73%).

10

<sup>1</sup>H NMR (DMSO) δ 12.15 (s, 1H), 8.64 (d, 2H), 8.43 (s, 1H), 8.03 (s, 1H), 7.90 (d, 2H), 7.63 (m, 2H), 7.43 (t, 1H), 6.92 (dd, 1H), 3.81 (s, 3H), 3.53 (m, 1H), 1.37 (d, 6H) ppm; ES-MS m/z 388 (MH<sup>+</sup>). Anal. calcd. for C<sub>21</sub>H<sub>21</sub>N<sub>7</sub>O; C: 65.1%; H: 5.5%; N: 25.3%. Found; C: 65.32%; H: 5.33%; N: 25.53%.

15

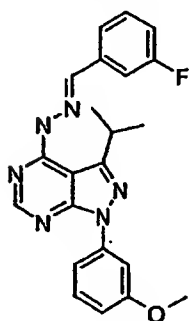
**Example 179****4-(Methylsulfonyl)benzaldehyde [3-isopropyl-1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone**

- 5 To a stirred solution of 4-hydrazino-3-isopropyl-1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine (Intermediates Example LL) (100 mg, 0.335 mmol) in ethanol (3 ml) was added 4-(methylsulfonyl)benzaldehyde (89.7 mg, 0.487 mmol) and pyrrolidine. The resulting mixture was refluxed for ca. 3 hours, cooled to RT, and filtered to give the product as a white solid (104.8 mg, 67%).

10

<sup>1</sup>H NMR (DMSO) δ 12.13 (s, 1H), 8.53 (s, 1H), 8.22 (d, 2H), 8.02 (s, 1H), 7.97 (d, 2H), 7.63 (m, 2H), 7.43 (t, 1H), 6.92 (dd, 1H), 3.81 (s, 3H), 3.55 (m, 1H), 3.23 (s, 3H), 1.37 (d, 6H) ppm; ES-MS m/z 465 (MH<sup>+</sup>). Anal. calcd. for C<sub>23</sub>H<sub>24</sub>N<sub>6</sub>O<sub>3</sub>S; C: 59.5%; H: 5.2%; N: 18.1%. Found; C: 59.39%; H: 5.22%; N: 17.51%.

15

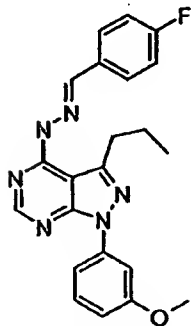
Example 1803-Fluorobenzaldehyde [3-isopropyl-1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone

- 5 To a stirred solution of 4-hydrazino-3-isopropyl-1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine (Intermediates Example LL) (100 mg, 0.335 mmol) in ethanol (3 ml) was added 3-fluorobenzaldehyde (54 mL, 0.503 mmol) and pyrrolidine. The resulting mixture was refluxed for ca. 3 hours, cooled to RT, and filtered to give the product as a white solid (75.7 mg, 56%).

10

<sup>1</sup>H NMR (DMSO) δ 12.06 (s, 1H), 8.45 (s, 1H), 7.95 (m, 2H), 7.71 (d, 1H), 7.62 (d, 2H), 7.46 (m, 1H), 7.44 (m, 1H), 7.22 (t, 1H), 6.92 (dd, 1H), 3.81 (s, 3H), 3.48 (m, 1H), 1.36 (d, 6H) ppm; ES-MS m/z 405 (MH<sup>+</sup>). Anal. calcd. for C<sub>22</sub>H<sub>21</sub>FN<sub>5</sub>O; C: 65.3%; H: 5.2%; N: 20.8%. Found; C: 65.21%; H: 5.25%; N: 20.76%.

15

**Example 181****4-Fluorobenzaldehyde [1-(3-methoxyphenyl)-3-propyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone**

5

To a stirred solution of 4-hydrazino-1-(3-methoxyphenyl)-3-propyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (Intermediates Example KK) (100 mg, 0.335 mmol) in ethanol (2 ml) was added 4-fluorobenzaldehyde (0.075 mL, 0.699 mmol) and pyrrolidine. The resulting mixture was refluxed for ca. 3 hours, cooled to RT, and filtered to give the product as a white solid (75 mg, 55%).

10

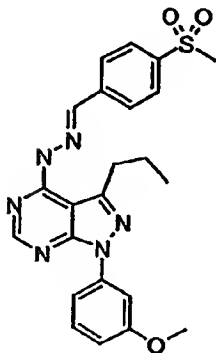
<sup>1</sup>H NMR (DMSO) δ 11.98 (d, 1H), 8.41 (s, 1H), 8.02 (dd, 2H), 7.93 (d, 1H), 7.62 (m, 2H), 7.41 (t, 1H), 7.29 (m, 2H), 6.90 (dd, 1H), 3.80 (s, 3H), 2.90 (t, 2H), 1.78 (q, 2H), 0.97 (t, 3H), 2.41 (s, 3H) ppm; ES-MS *m/z* 405 (MH<sup>+</sup>). Anal. calcd for C<sub>22</sub>H<sub>21</sub>FN<sub>5</sub>O; C: 65.3%;

15 H: 5.2%; N: 20.8%. Found; C: 65.31%; N: 5.34%; N: 20.83%.

270

**Example 182**

**4-(Methylsulfonyl)benzaldehyde [1-(3-methoxyphenyl)-3-propyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone**

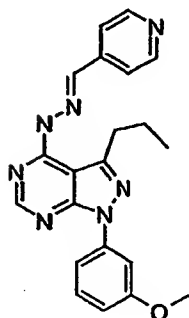


5

To a stirred solution of 4-hydrazino-1-(3-methoxyphenyl)-3-propyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (Intermediates Example KK) (100 mg, 0.335 mmol) in ethanol (2 ml) was added 4-(methylsulfonyl)benzaldehyde (123 mg, 0.668 mmol) and pyrrolidine. The resulting mixture was refluxed for ca. 3 hours, cooled to RT, and filtered to give the product as a white solid (121 mg, 78%).

<sup>1</sup>H NMR (DMSO) δ 12.15 (s, 1H), 8.50 (s, 1H), 8.21 (d, 2H), 8.00 (d, 1H), 7.96 (d, 2H), 7.62 (m, 2H), 7.41 (t, 1H), 6.91 (dd, 1H), 3.81 (s, 3H), 3.25 (s, 3H), 2.93 (t, 2H), 1.79 (q, 2H), 0.98 (t, 3H) ppm; ES-MS *m/z* 465 (MH<sup>+</sup>). Anal. calcd. for C<sub>23</sub>H<sub>24</sub>N<sub>6</sub>O<sub>3</sub>S; C: 59.5%; H: 5.2%; N: 18.1%. Found; C: 59.29%; H: 5.29%; N: 17.83%.

20

**Example 183****Isonicotinaldehyde [1-(3-methoxyphenyl)-3-propyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone**

To a stirred solution of 4-hydrazino-1-(3-methoxyphenyl)-3-propyl-1H-pyrazolo[3,4-d]pyrimidine (Intermediates Example KK) (52 mg, 0.22 mmol) in ethanol (5 ml) was added isonicotinaldehyde (63 mL, 0.669 mmol) and pyrrolidine. The resulting mixture was refluxed for ca. 3 hours, cooled to RT, and filtered to give the product as a white solid (88 mg, 68%).

10

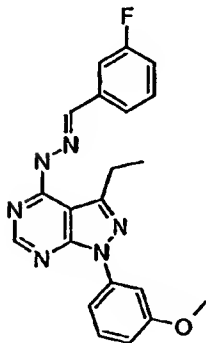
<sup>1</sup>H NMR (DMSO) δ 12.15 (s, 1H), 8.63, (d, 2H), 8.41 (s, 1H), 8.01 (s, 1H), 7.90 (d, 2H), 7.62 (m, 2H), 7.41 (t, 1H), 6.91 (dd, 1H), 3.81 (s, 3H), 2.92 (t, 2H), 1.80 (m, 2H), 0.97 (t, 3H) ppm; ES-MS m/z 388 (MH<sup>+</sup>); anal. calcd. for C<sub>21</sub>H<sub>21</sub>N<sub>5</sub>O: C; 65.1%; H: 5.5%; N: 25.3%. Found: C: 65.31%; H: 5.36%; N: 25.60%.

15



**Example 184**

3-fluorobenzaldehyde [3-ethyl-1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone

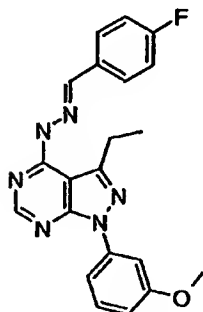


5

To a stirred solution of 4-hydrazino-1-(3-methoxyphenyl)-3-ethyl-1H-pyrazolo[3,4-d]pyrimidine (Intermediates Example MM) (100 mg, 0.35 mmol) in ethanol (10 ml) was added 3-fluorobenzaldehyde (75  $\mu$ L, 0.70 mmol) and pyrrolidine. The resulting mixture was refluxed for ca. 18 hours, cooled to RT, and concentrated. The residue was purified by silica gel flash chromatography (20% ethyl acetate in hexanes) to give the product as a white solid (76 mg, 56%).

<sup>1</sup>H NMR (DMSO)  $\delta$  12.06 (s, 1H), 8.43 (m, 1H), 7.93 (m, 2H), 7.65 (m, 3H), 7.45 (m, 2H), 7.23 (t, 1H), 6.92 (dd, 1H), 3.81 (s, 3H), 2.95 (q, 2H), 1.31 (t, 3H) ppm; ES-MS  $m/z$  391 (MH<sup>+</sup>).

15

Example 1854-fluorobenzaldehyde [3-ethyl-1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone

5

To a stirred solution of 4-hydrazino-1-(3-methoxyphenyl)-3-ethyl-1H-pyrazolo[3,4-d]pyrimidine (Intermediates Example MM) (100 mg, 0.35 mmol) in ethanol (10 ml) was added 4-fluorobenzaldehyde (58  $\mu$ L, 0.70 mmol) and pyrrolidine. The resulting mixture was refluxed for ca. 18 hours, cooled to RT, and concentrated. The residue was purified by silica gel flash chromatography (10% ethyl acetate  $\rightarrow$  20% ethyl acetate in hexanes) to give the product as a white solid (95 mg, 69%).

10

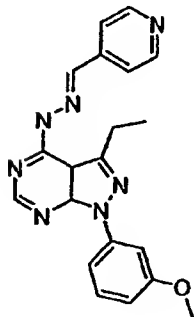
$^1\text{H}$  NMR (DMSO)  $\delta$  12.00 (s, 1H), 8.43 (m, 1H), 8.01 (m, 2H), 7.61 (m, 2H), 7.40 (m, 3H), 6.90 (m, 1H), 6.60 (m, 1H), 3.80 (s, 3H), 2.94 (q, 2H), 1.30 (t, 3H) ppm; ES-MS  $m/z$  391 (MH $^+$ ).

15

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**Example 186**

**Isonicotinaldehyde [3-ethyl-1-(3-methoxyphenyl)-3a,7a-dihydro-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hydrazone**



5

To a stirred solution of 4-hydrazino-1-(3-methoxyphenyl)-3-ethyl-1H-pyrazolo[3,4-d]pyrimidine (Intermediates Example MM) (100 mg, 0.35 mmol) in ethanol (10 ml) was added isonicotinaldehyde (67  $\mu$ L, 0.70 mmol) and pyrrolidine. The resulting mixture was refluxed for ca. 18 hours, cooled to RT, and filtered to give the product as a white solid (76 mg, 58%).

$^1\text{H}$  NMR (DMSO)  $\delta$  12.16 (s, 1H), 8.64, (d, 2H), 8.43(s, 1H), 8.02 (s, 1H), 7.91 (m, 2H), 7.63 (m, 2H), 7.42 (t, 1H), 6.93 (dd, 1H), 3.81 (s, 3H), 2.97 (q, 2H), 1.31 (t, 3H) ppm; ES-MS  $m/z$  374 ( $\text{MH}^+$ ); anal. calcd. for  $\text{C}_{20}\text{H}_{19}\text{N}_7\text{O}$ ; C: 64.3%; H: 5.1%; N: 26.3%. Found: C: 64.10%; H: 5.01%; N: 26.20%.

20

BIOLOGICAL DATAGSK-3

5           The compounds of the present invention elicit important and measurable pharmacological responses. In evaluating those responses, the present invention also demonstrated unexpected advantageous biological and pharmacological properties. In short, the present invention provides unexpected superior performance characteristics not heretofore appreciated.

10           The protocol used to demonstrate the pharmacological response of the present invention is based on the ability of the kinase to phosphorylate a biotinylated peptide, the sequence of which is derived from the phosphorylation site of glycogen synthase and its sequence is: Biotin-Ahx-AAAKRREILSRPS(PO<sub>3</sub>)YR-amide. The phosphorylated biotinylated peptide is then captured onto streptavidin coated scintillation proximity  
15 assay (SPA) beads from Amersham Technology, where the signal from the <sup>32</sup>P is amplified via the scintillant contained in the beads.

          GSK-3 $\beta$  is commercially available or may be cloned and expressed in E coli using standard techniques to produce soluble, active protein. The production of active protein involves purification in two steps using Metal Chelate and Ion Exchange  
20 Chromatography. Protein eluting from Ion Exchange provides >90% pure product that may then be concentrated for use in high throughput screening.

          The kinase was assayed at a concentration of 20 nM final in 100 mM HEPES, pH 7.2 containing 10 mM magnesium chloride, 0.1 mg/mL bovine serum albumin, 1mM dithiothreitol, 0.3 mg/mL heparin, 2.8uM peptide substrate, 2.5uM ATP, and  
25 0.2uCi/well [<sup>32</sup>P]-ATP. After 40 minutes incubation at room temperature, the reaction was stopped by addition of 100mM EDTA and 1mM solution in 100mM HEPES, pH7.2 followed by an additional solution of diluted Streptavidin coated SPA beads in PBS, pH 7.2 to give a final concentration of 0.25 mg of beads per assay well in a 96-well microtiter plate.

30           10 mM stock solutions of the compounds of the invention in 100% DMSO are generated as a first step in the screening process. The second step involves the creation of dose response plates where these compounds are diluted 10-fold in 100%

DMSO to 1 mM concentrations and subsequently serially diluted 3-fold in 100% DMSO across the plate by automated liquid handling such that the final top concentration of inhibitor is 0.033 mM in the 30 uL kinase assay. The third step involves the creation of the assay plates. This is achieved by transferring 1 uL of the compounds to assay  
5 plates by automated liquid handling. The fourth step is to perform the assay as described and count the resulting plates in the Packard TopCount NXT microplate scintillation and luminescence counter.

The final step is data acquisition and analysis where  $IC_{50}$  values are generated for each compound by normalizing curve data to the equation  $100 \cdot (U1 - C2) / (C1 - C2)$   
10 (where U1 is the cpm value, C2 is the background, and C1 is the maximum number of counts), then fitting the normalized data to the equation  $y = V_{max} \cdot (1 - (x / (K + x)))$ . The  $IC_{50}$  values were converted to  $pIC_{50}$  values, i.e.,  $-\log IC_{50}$  in Molar concentration. The data is expressed below in Table 1.

Test compounds are employed in free or salt form.

277

TABLE 1

<u>Example</u>	<u>GSK3 pIC50</u>
1	+
2	+
3	+
4	++
5	+++
6	++
7	+++
8	+
9	++
11	+
12	++
13	+++
14	+++
15	++
16	++
17	+
18	+
19	+
21	+
22	+
23	+
24	++
26	++
27	+
28	++
29	++
30	+
31	++
32	+

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33	+
34	+
35	+++
36	++
38	++
40	+
42	++
43	+
44	++
46	+
47	+
48	++
49	+
50	+

<u>Example</u>	<u>GSK3 pIC50</u>
----------------	-------------------

51	+
52	++
53	++
54	++
55	++
56	++
57	++
58	++
59	++
60	
61	++
62	++
63	+
64	+++
65	+
66	++

279

67	++
68	+++
69	++
70	+++
71	++
72	+++
73	+++
75	+++
76	++
77	+++
78	+++
79	+++
80	+++
81	+++
82	++
83	+++
84	+++
85	+++
86	+++
87	+++
88	+++
89	+++
90	+++
91	++
92	+
93	+++
94	+++
95	+++
96	+++

<u>Example</u>	<u>GSK3 pIC50</u>
----------------	-------------------

97	++
----	----



280

98	+++
99	+++
100	+
101	+++
102	+++
103	+++
104	+++
105	+++
106	+++
107	+++
108	+++
109	+++
110	+++
111	+++
113	+++
114	+++
115	+++
116	+++
117	+++
118	+++
119	+++
120	+++
121	+++
122	++
123	+++
124	++
125	++
126	+++
127	+++
128	+++
129	++

281

130	+++
131	+++
132	++
133	+
134	++
135	+++
136	++
137	++
138	+++
139	++
140	+++
141	+++

<u>Example</u>	<u>GSK3 pIC50</u>
----------------	-------------------

142	+++
143	+
144	+++
145	+++
146	+++
147	+++
148	+++
149	+++
150	+++
151	+++
152	+++
153	+
154	+++
155	+++
156	+++
157	++
158	+++

282

159	+++
160	+
161	+++
163	++
164	+++
165	+++
166	+++
168	+++
169	+++
170	+++
171	+++
172	++
173	+++
174	+++
175	++
176	+++
177	+++
178	+++
179	++
180	+++
181	+++
182	++
183	+++
184	+++
185	+++
186	+++

+ = pIC<sub>50</sub> of 5.0 – 6.0; ++ = pIC<sub>50</sub> of 6.0 – 7.0; +++ = pIC<sub>50</sub> of > 7.0.

TIE-2 Enzyme assay (TIE2-E)

The TIE-2 enzyme assay used the LANCE method (Wallac) and GST-TIE2, baculovirus expressed recombinant constructs of the intracellular domains of human TIE2 (amino acids 762-1104, GenBank Accession # L06139) tagged by GST). The method measured the ability of the purified enzymes to catalyse the transfer of the  $\gamma$ -phosphate from ATP onto tyrosine residues in a biotinylated synthetic peptide, D1-15 (biotin-C6-LEARLVAYEGWVAGKKKamide). This peptide phosphorylation was detected using the following procedure: for enzyme preactivation, GST-TIE2 was incubated for 30mins at room temperature with 2 mM ATP, 5 mM MgCl<sub>2</sub> and 12.5 mM DTT in 22.5 mM HEPES buffer (pH7.4). Preactivated GST-TIE2 was incubated for 30mins at room temperature in 96 well plates with 1  $\mu$ M D1-15 peptide, 80  $\mu$ M ATP, 10 mM MgCl<sub>2</sub>, 0.1mg/ml BSA and the test compound (diluted from a 10 mM stock in DMSO, final DMSO concentration was 2.4%) in 1 mM HEPES (pH7.4). The reaction was stopped by the addition of EDTA (final concentration 45 mM). Streptavidin linked-APC (allophycocyanin, Molecular Probe) and Europium-labeled anti-phosphorylated tyrosine antibody (Wallac) were then added at the final concentration of 17  $\mu$ g/well and 2.1  $\mu$ g/well, respectively. The APC signal was measured using an ARVO multilabel counter. (Wallac Berthold Japan). The percent inhibition of activity was calculated relative to blank control wells.

*Tie2 fluorescence polarization kinase activity assay: (TIE2-FP)**Activation of recombinant Tie2 activation:*

Recombinant GST-Tie2 was activated by incubating the enzyme in 20 mM Tris-HCl, pH 7.5, 12 mM MgCl<sub>2</sub>, 100 mM NaCl, 20  $\mu$ M sodium vanadate, 1 mM DTT and 300  $\mu$ M ATP at room temperature for 2 hours. The activation mixture was then passed through a NAP-25 desalting column (Pharmacia Biotech cat. no. 17-0852-02) to remove the free ATP. The activated enzyme was stored as aliquots at -80°C in 20mM Tris-HCl, pH 7.5 and 100 mM NaCl.

*Assay conditions:*

The final assay conditions were 50 mM HEPES, pH 7.5, 5% DMSO (when screening compounds), 200  $\mu$ M ATP, 5 mM  $MgCl_2$ , 1 mM DTT, 50  $\mu$ M sodium vanadate, 1 nM activated enzyme, and 200  $\mu$ M peptide.  $IC_{50}$ 's of compounds were measured under subsaturating ATP (200  $\mu$ M) and varying concentrations of activated Tie2 and peptide substrate (RFWKYEFWR-OH; MW 1873 Da, TFA salt). Panvera Anti-phosphotyrosine antibody (Cat#P2840) and PTK Green Tracer (Cat#P2842) were used to detect the phosphorylated peptide. Polarization was measured on a TECAN Polarion in 138-second cycles for 30 minutes at room temperature.  $IC_{50}$ 's were then determined from the % polarization using normal calculation methods. Results are indicated at Table 2 below.

The concentration of test compound that inhibits 50% of activity ( $IC_{50}$ ) was interpolated using nonlinear regression (Levenberg-Marquardt) and the equation,  $y = V_{max} (1-x/(K+x)) + Y_2$ , where "K" was equal to the  $IC_{50}$ . The  $IC_{50}$  values were converted to  $pIC_{50}$  values, i.e.,  $-\log IC_{50}$  in Molar concentration. The results are represented in Table 2 below.

Test compounds are employed in free or salt form.

TABLE 2

Example #	TIE2-E	TIE2-FP
12	+	
52	+	
54	+++	
55	++	
56	++	
57	++	
58	++	
61	++	
63	+	
64	++	
66	+	

285

67	++	
68	+	
69	+	
70	++	
71	++	
99		++
101		++
102		++
114		+
115		++
116		++
152	++	
153	++	
154	++	
180	+	

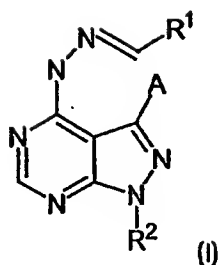
+ = pIC<sub>50</sub> of 5.0 – 6.0; ++ = pIC<sub>50</sub> of 6.0 – 7.0; +++ = pIC<sub>50</sub> of > 7.0;

Although specific embodiments of the present invention have been illustrated  
 5 and described in detail, it is to be expressly understood that the invention is not  
 limited thereto. The above detailed description of the embodiment is provided for  
 example only and should not be construed as constituting any limitation of the  
 invention. Modifications will be obvious to those skilled in the art, and all  
 modifications that do not depart from the spirit of the invention are intended to be  
 10 included within the scope of the appended claims.

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What is claimed is:

1. A compound of Formula (I)

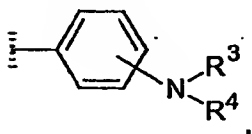


including salts, solvates, and pharmaceutically acceptable derivatives thereof,

wherein A is H, alkyl, or aryl;

R<sup>1</sup> is D<sup>1</sup>, D<sup>2</sup>, D<sup>3</sup>, D<sup>4</sup>, or D<sup>5</sup>,

wherein D<sup>1</sup> is



and R<sup>3</sup> and R<sup>4</sup> are each independently H, alkyl, alkylsulfonyl, or -C(O)-(CH<sub>2</sub>)<sub>x</sub>-R<sup>5</sup>,

where R<sup>5</sup> is alkyl, acyl, alkoxy, -(O)-(CH<sub>2</sub>)<sub>x</sub>-(O)-alkyl, or -NR<sup>6</sup>R<sup>7</sup>,

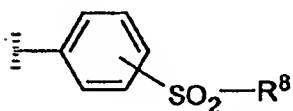
where R<sup>6</sup> and R<sup>7</sup> are each independently H or alkyl, or

R<sup>6</sup> and R<sup>7</sup> combine to form a 5- or 6-membered ring, optionally containing one or more additional heteroatoms, optionally containing

one or more degrees of unsaturation, and optionally substituted one or more times with alkyl, hydroxy, carboxy, acyl, alkoxy, or halogen,

or R<sup>3</sup> and R<sup>4</sup> combine to form a 5- or 6-membered ring, optionally containing one or more additional heteroatoms, optionally containing one or more degrees of unsaturation, and optionally substituted one or more times with alkyl, hydroxy, carboxy, alkoxy, acyl, or halogen;

wherein D<sup>2</sup> is



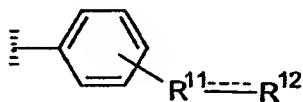
and R<sup>8</sup> is alkyl, or -NR<sup>9</sup>R<sup>10</sup>,

where R<sup>9</sup> and R<sup>10</sup> are each independently selected from H, alkyl, or -(CH<sub>2</sub>)<sub>x</sub>-NR<sup>6</sup>R<sup>7</sup>,

where R<sup>6</sup> and R<sup>7</sup> are each independently H or alkyl,

or R<sup>6</sup> and R<sup>7</sup> combine to form a 5- or 6-membered ring, optionally containing one or more additional heteroatoms, optionally containing one or more degrees of unsaturation, and optionally substituted one or more times with alkyl, hydroxy, carboxy, acyl, alkoxy, or halogen;

wherein D<sup>3</sup> is



and

the dashed line represents an optional double bond;



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when  $R^{11}$  is  $-(CH_2)_x$ , the optional dashed double bond does not exist, and  $R^{12}$  is alkylsulfonyl or  $-NR^{13}R^{14}$ ,

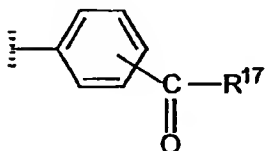
where  $R^{13}$  and  $R^{14}$  are each independently selected from H, alkyl,  $-(CH_2)_x-R^{17}$ , where  $R^{17}$  is alkoxy or  $-NR^{15}R^{16}$ ,

where  $R^{15}$  and  $R^{16}$  are each independently H or alkyl,

or  $R^{13}$  and  $R^{14}$  combine to form a 5- or 6-membered ring, optionally containing one or more additional heteroatoms, optionally containing one or more degrees of unsaturation, and optionally substituted one or more times with alkyl or  $-(CH_2)_x-OH$ ;

when  $R^{11}$  is  $-(CH)-$ , the optional dashed double bond exists, and  $R^{12}$  is  $-(CH)-C(O)-OH$ ;

wherein  $D^4$  is



and  $R^{17}$  is hydroxy, alkoxy, or  $-NR^{18}R^{19}$ ,

where  $R^{18}$  and  $R^{19}$  are each independently selected from H, alkyl,  $-(CH_2)_x-R^{20}$ ,

where  $R^{20}$  is alkylsulfonyl, hydroxy, aryl said aryl optionally substituted with hydroxy or alkoxy, heteroaryl, or  $-NR^{21}R^{22}$ ,

where  $R^{21}$  and  $R^{22}$  are each independently selected from H, acyl, alkyl,

or R<sup>21</sup> and R<sup>22</sup> combine to form a 5- or 6-membered ring, optionally containing one or more additional heteroatoms, optionally containing one or more degrees of unsaturation, and optionally substituted with alkyl or  $-(CH_2)_x-OH$ ;

or R<sup>18</sup> and R<sup>19</sup> combine to form a 5- or 6-membered ring, optionally containing one or more additional heteroatoms, optionally containing one or more degrees of unsaturation, and optionally substituted with  $-(CH_2)_x-R^{23}$ ,

where R<sup>23</sup> is alkoxy, hydroxy,  $-C(O)-R^{24}$ , where R<sup>24</sup> is a 5- or 6-membered ring optionally containing one or more heteroatoms and optionally containing one or more degrees of unsaturation, or  $-NR^{25}R^{26}$ , where R<sup>25</sup> and R<sup>26</sup> are each independently H or alkyl;

wherein D<sup>5</sup> is

a 5- or 6- membered ring, optionally containing one or more heteroatoms, optionally containing one or more degrees of unsaturation, optionally fused with an additional 5- or 6- membered ring that optionally contains one or more heteroatoms and optionally contains one or more degrees of unsaturation,

wherein the ring or fused ring system may be optionally substituted one or more times with halogen, alkyl, haloalkyl, alkylsulfonyl, alkylthio, hydroxy, alkoxy, oxo, sulfonyl, sulfate ion, nitro, cyano, carboxy, alkoxycarbonyl, aryl where said aryl may be optionally substituted with sulfamoyl, heteroaryl where said heteroaryl may be optionally substituted with alkyl, or  $-NR^{27}R^{28}$ ,

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where  $R^{27}$  and  $R^{28}$  are each independently H, alkyl, acyl, alkoxy, alkoxy carbonyl, carboxy, or  $-(CH_2)_x-NR^{29}R^{30}$ , where  $R^{29}$  and  $R^{30}$  are each independently selected from H and alkyl,

or  $R^{27}$  and  $R^{28}$  combine to form a 5- or 6- membered ring, optionally containing one or more additional heteroatoms, optionally containing one or more degrees of unsaturation, and optionally substituted one or more times with alkyl, hydroxy, carboxy, acyl, alkoxy, or halogen,

or  $-(O)_y-(CH_2)_x-R^{31}$ , where  $R^{31}$  is hydroxy, alkoxy, haloalkyl, aryl optionally substituted with halogen, or  $-NR^{27}R^{28}$ , where  $R^{27}$  and  $R^{28}$  are as defined above;

wherein for each occurrence, x independently is 0, 1, 2, or 3;

wherein for each occurrence, y independently is 0 or 1; and

$R^2$  is phenyl, substituted one or more times with alkyl, alkoxy, halogen, haloalkyl, haloalkoxy, nitro, or  $-NR^{31}R^{32}$ ,

wherein  $R^{31}$  and  $R^{32}$  are each independently selected from H, alkyl, acyl, or  $-(CH_2)_z-R^{33}$ ,

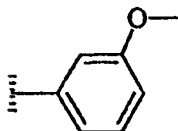
where z is 0, 1, or 2;

and  $R^{33}$  is cycloalkyl.

2. The compound of claim 1 wherein  $R^1$  is  $D^5$ .
3. The compound of claim 2 wherein  $D^5$  is pyridyl.
4. The compound of claim 3, wherein  $D^5$  is 4-pyridyl.
5. The compound of claim 1 wherein  $R^2$  is phenyl substituted with alkoxy.

6. The compound of claim 5 wherein the alkoxy is methoxy.

7. The compound of claim 6 wherein R<sup>2</sup> is



8. The compound of claim 1 wherein for each occurrence, said alkyl is C<sub>1</sub>-C<sub>6</sub> alkyl.

9. The compound of claim 1 wherein R<sup>1</sup> is D<sup>3</sup> and R<sup>11</sup> and R<sup>12</sup> combine to form  
-(CH)=(CH)-C(O)-OH.

10. The compound of claim 9 wherein the stereochemical configuration is *cis*.

11. The compound of claim 9 wherein the stereochemical configuration is *trans*.

12. The compound of claim 1 wherein A is H.

13. The compound of claim 1 wherein A is alkyl.

14. The compound of claim 13 wherein A is C<sub>1-6</sub> alkyl.

15. The compound of claim 14 wherein A is selected from propyl or isopropyl.

16. A pharmaceutical composition comprising:

a therapeutically effective amount of a compound as claimed in claims 1 to 15.

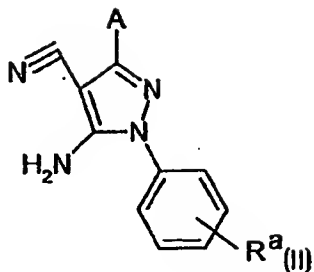
17. The pharmaceutical composition of claim 16 further comprising:

one or more of pharmaceutically acceptable carriers, diluents, or excipients.

18. A method of treating a disorder in a mammal, said disorder being characterized by misregulation of one or more protein kinase comprising:  
administering to said mammal a therapeutically effective amount of a compound as claimed in claims 1 to 15.
19. The method of claim 18 wherein the kinase is a serine/threonine kinase.
20. The method of claim 19 wherein the kinase is GSK3.
21. The method of claim 18 wherein the kinase is a tyrosine kinase.
22. The method of claim 21 wherein the kinase is TIE2.
23. A method of treating a disorder in a mammal, said disorder being characterized by misregulation of one or more protein kinase, comprising:  
administering to said mammal a therapeutically effective amount of a compound as claimed in claims 1 to 15.
24. The method of claim 23 wherein the protein kinase is GSK3.
25. The method of claim 23 wherein the protein kinase is TIE2.
26. A compound as claimed in claims 1 to 15 for use in therapy.
27. Use of a compound as claimed in claims 1 to 15 in the preparation of a medicament for use in the treatment of a disorder characterized by misregulation of one or more protein kinase.

28. A method of treating type 2 diabetes, hyperlipidemia, obesity, CNS disorders, neurotraumatic injuries, immune potentiation, baldness or hair loss, atherosclerotic cardiovascular disease, hypertension, polycystic ovary syndrome, ischemia, immunodeficiency, and cancer, comprising:  
administering to said mammal a therapeutically effective amount of a compound as claimed in claims 1 to 15.
29. A method of treating type II diabetes, comprising:  
administering to said mammal therapeutically effective amounts of
- (i) a compound as claimed in claims 1 to 15; and
  - (ii) at least one additional anti-diabetic agent.
30. A compound according to any of claims 1 to 15 with reference to any of the Examples.
-

31. A compound of Formula (II):



including salts, solvates, and pharmaceutically functional derivatives thereof,

where A is H, alkyl, or aryl;

R<sup>a</sup> is alkyl, alkoxy, halogen, haloalkyl, haloalkoxy, nitro, or -NR<sup>b</sup>R<sup>c</sup>,

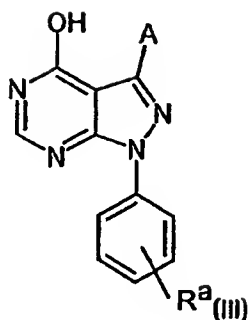
wherein R<sup>b</sup> and R<sup>c</sup> are each independently selected from H, alkyl, acyl, or -(CH<sub>2</sub>)<sub>z</sub>-R<sup>d</sup>,

where z is 0, 1, or 2; and

R<sup>d</sup> is cycloalkyl.

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32. A compound of formula (III)



including salts, solvates, and pharmaceutically functional derivatives thereof,

where A is H, alkyl, or aryl;

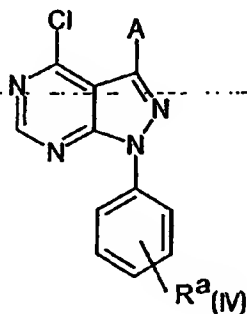
$R^a$  is alkyl, alkoxy, halogen, haloalkyl, haloalkoxy, nitro, or  $-NR^bR^c$ ,

wherein  $R^b$  and  $R^c$  are each independently selected from H, alkyl, acyl, or  $-(CH_2)_z-$   
 $R^d$ ,

where z is 0, 1, or 2; and

$R^d$  is cycloalkyl.

33. A compound of formula (IV)



including salts, solvates, and pharmaceutically functional derivatives thereof,

where A is H, alkyl, or aryl;

$R^a$  is alkyl, alkoxy, halogen, haloalkyl, haloalkoxy, nitro, or  $-NR^bR^c$ ,



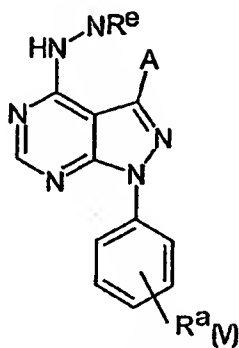
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wherein  $R^b$  and  $R^c$  are each independently selected from H, alkyl, acyl, or  $-(CH_2)_z-$   
 $R^d$ ,

where  $z$  is 0, 1, or 2; and

$R^d$  is cycloalkyl.

34. A compound of formula (V)



including salts, solvates, and pharmaceutically functional derivatives thereof,

where A is H, alkyl, or aryl;

$R^e$  is alkyl, alkoxy, halogen, haloalkyl, haloalkoxy, nitro, or  $-NR^bR^c$ ,

wherein  $R^b$  and  $R^c$  are each independently selected from H, alkyl, acyl, or  $-(CH_2)_z-$   
 $R^d$ ,

where  $z$  is 0, 1, or 2;

$R^d$  is cycloalkyl; and

$R^e$  is H or  $-C(O)-(O)-C-(CH_3)_3$ .

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 03/22716

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D487/04 C07D519/00 A61K31/519 A61P3/10  
 //(C07D487/04, 239:00, 231:00)

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, EPO-Internal, PAJ, WPI Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 1 040 831 A (PFIZER PROD INC) 4 October 2000 (2000-10-04) page 2, line 54 - line 55 page 3, formula II	1-34
A	WO 02 055082 A (LERPINIERE JOANNE ; GAUR SUNEEL (GB); GILLESPIE ROGER JOHN (GB); VE) 18 July 2002 (2002-07-18) page 1, line 9 page 1, line 14 - line 15 page 6, formula (I) page 18, line 30 - line 33 pages 28-34, Table 1	1-34
-/-		

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- \*&\* document member of the same patent family

Date of the actual completion of the international search

5 December 2003

Date of mailing of the international search report

17/12/2003

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Hoepfner, W

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 03/22716

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 01 19829 A (BASF AG ;HIRST GAVIN C (US); RAFFERTY PAUL (US); RITTER KURT (US);) 22 March 2001 (2001-03-22) page 14, formula I page 44, line 14 page 45, line 15 page 46, line 8 - line 9	1-34
A	WO 02 50065 A (EVERITT SIMON ;KAY DAVID (GB); KNEGTEL RONALD (GB); PATEL SANJAY ()) 27 June 2002 (2002-06-27) page 6, formula I page 20, line 10 page 201, partial structure IVd-V	1-34

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US 03/22716

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(e) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Although claims 18-26, 28 and 29 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 03/22716

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 1040831	A	04-10-2000	AU 761694 B2	05-06-2003
			AU 2263400 A	05-10-2000
			CA 2303577 A1	02-10-2000
			EP 1040831 A2	04-10-2000
			HU 0001358 A2	29-01-2001
			JP 2000302693 A	31-10-2000
			US 6384039 B1	07-05-2002
			ZA 200001610 A	01-10-2001
WO 02055082	A	18-07-2002	CA 2433997 A1	18-07-2002
			EP 1349552 A1	08-10-2003
			WO 02055082 A1	18-07-2002
WO 0119829	A	22-03-2001	AT 247657 T	15-09-2003
			AU 7495000 A	17-04-2001
			BG 106586 A	31-01-2003
			BR 0014073 A	16-07-2002
			CA 2385747 A1	22-03-2001
			CN 1390220 T	08-01-2003
			CZ 20020936 A3	16-10-2002
			DE 60004685 D1	25-09-2003
			EP 1212327 A2	12-06-2002
			JP 2003509428 T	11-03-2003
			NO 20021328 A	21-05-2002
			TR 200201505 T2	21-01-2003
			WO 0119829 A2	22-03-2001
			US 2002156081 A1	24-10-2002
WO 0250065	A	27-06-2002	AU 3116602 A	01-07-2002
			AU 3404702 A	01-07-2002
			AU 9091201 A	26-03-2002
			AU 9091401 A	26-03-2002
			AU 9094401 A	26-03-2002
			AU 9101301 A	26-03-2002
			AU 9267001 A	26-03-2002
			AU 9455801 A	26-03-2002
			AU 9687101 A	26-03-2002
			AU 9687501 A	26-03-2002
			BR 0114088 A	17-06-2003
			BR 0116411 A	11-11-2003
			BR 0116493 A	30-09-2003
			CA 2422299 A1	21-03-2002
			CA 2422354 A1	21-03-2002
			CA 2422367 A1	21-03-2002
			CA 2422371 A1	21-03-2002
			CA 2422377 A1	21-03-2002
			CA 2422378 A1	21-03-2002
			CA 2422379 A1	21-03-2002
			CA 2422380 A1	21-03-2002
			CA 2432129 A1	25-07-2002
			CA 2432131 A1	01-08-2002
			CA 2432132 A1	01-08-2002
			CA 2432222 A1	15-08-2002
			CA 2432223 A1	06-09-2002
			CA 2432303 A1	29-08-2002
			CA 2432799 A1	27-06-2002
			CA 2432872 A1	27-06-2002
			EP 1345922 A1	24-09-2003

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 03/22716

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0250065 A		EP 1355905 A1	29-10-2003
		EP 1317447 A1	11-06-2003
		EP 1317444 A1	11-06-2003
		EP 1317448 A1	11-06-2003
		EP 1318997 A1	18-06-2003
		EP 1317449 A1	11-06-2003
		EP 1317450 A1	11-06-2003
		EP 1317452 A1	11-06-2003
		EP 1318814 A2	18-06-2003
		EP 1345925 A2	24-09-2003
		EP 1345928 A2	24-09-2003
		EP 1345926 A2	24-09-2003
		EP 1353916 A2	22-10-2003
		EP 1345929 A2	24-09-2003
		EP 1345927 A1	24-09-2003
		HU 0302172 A2	29-09-2003
		HU 0302173 A2	29-09-2003
		NO 20031188 A	13-05-2003
		NO 20031189 A	13-05-2003

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 03/22716

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 7 C07D487/04 C07D519/00 A61K31/519 A61P3/10  
//(C07D487/04, 239:00, 231:00)

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

CHEM ABS Data, EPO-Internal, PAJ, WPI Data

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- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- \*Z\* document member of the same patent family

Date of the actual completion of the international search

5 December 2003

Date of mailing of the international search report

17/12/2003

Name and mailing address of the ISA

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Hoepfner, W

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 03/22716

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	WO 02 50065 A (EVERITT SIMON ;KAY DAVID (GB); KNEGTEL RONALD (GB); PATEL SANJAY ()) 27 June 2002 (2002-06-27) page 6, formula I page 20, line 10 page 201, partial structure IVd-V	1-34



# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US 03/22716

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

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because they relate to subject matter not required to be searched by this Authority, namely:  
  
Although claims 18-26, 28 and 29 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
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because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
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because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(e).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 03/22716

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 1040831	A	04-10-2000	AU 761694 B2	05-06-2003
			AU 2263400 A	05-10-2000
			CA 2303577 A1	02-10-2000
			EP 1040831 A2	04-10-2000
			HU 0001358 A2	29-01-2001
			JP 2000302693 A	31-10-2000
			US 6384039 B1	07-05-2002
			ZA 200001610 A	01-10-2001
WO 02055082	A	18-07-2002	CA 2433997 A1	18-07-2002
			EP 1349552 A1	08-10-2003
			WO 02055082 A1	18-07-2002
WO 0119829	A	22-03-2001	AT 247657 T	15-09-2003
			AU 7495000 A	17-04-2001
			BG 106586 A	31-01-2003
			BR 0014073 A	16-07-2002
			CA 2385747 A1	22-03-2001
			CN 1390220 T	08-01-2003
			CZ 20020936 A3	16-10-2002
			DE 60004685 01	25-09-2003
			EP 1212327 A2	12-06-2002
			JP 2003509428 T	11-03-2003
			NO 20021328 A	21-05-2002
			TR 200201505 T2	21-01-2003
			WO 0119829 A2	22-03-2001
			US 2002156081 A1	24-10-2002
WO 0250065	A	27-06-2002	AU 3116602 A	01-07-2002
			AU 3404702 A	01-07-2002
			AU 9091201 A	26-03-2002
			AU 9091401 A	26-03-2002
			AU 9094401 A	26-03-2002
			AU 9101301 A	26-03-2002
			AU 9267001 A	26-03-2002
			AU 9455801 A	26-03-2002
			AU 9687101 A	26-03-2002
			AU 9687501 A	26-03-2002
			BR 0114088 A	17-06-2003
			BR 0116411 A	11-11-2003
			BR 0116493 A	30-09-2003
			CA 2422299 A1	21-03-2002
			CA 2422354 A1	21-03-2002
			CA 2422367 A1	21-03-2002
			CA 2422371 A1	21-03-2002
			CA 2422377 A1	21-03-2002
			CA 2422378 A1	21-03-2002
			CA 2422379 A1	21-03-2002
			CA 2422380 A1	21-03-2002
			CA 2432129 A1	25-07-2002
			CA 2432131 A1	01-08-2002
			CA 2432132 A1	01-08-2002
			CA 2432222 A1	15-08-2002
			CA 2432223 A1	06-09-2002
			CA 2432303 A1	29-08-2002
			CA 2432799 A1	27-06-2002
			CA 2432872 A1	27-06-2002
			EP 1345922 A1	24-09-2003

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 03/22716

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WD 0250065	A	EP 1355905 A1	29-10-2003
		EP 1317447 A1	11-06-2003
		EP 1317444 A1	11-06-2003
		EP 1317448 A1	11-06-2003
		EP 1318997 A1	18-06-2003
		EP 1317449 A1	11-06-2003
		EP 1317450 A1	11-06-2003
		EP 1317452 A1	11-06-2003
		EP 1318814 A2	18-06-2003
		EP 1345925 A2	24-09-2003
		EP 1345928 A2	24-09-2003
		EP 1345926 A2	24-09-2003
		EP 1353916 A2	22-10-2003
		EP 1345929 A2	24-09-2003
		EP 1345927 A1	24-09-2003
		HU 0302172 A2	29-09-2003
		HU 0302173 A2	29-09-2003
		NO 20031188 A	13-05-2003
		NO 20031189 A	13-05-2003